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March 1, 2000

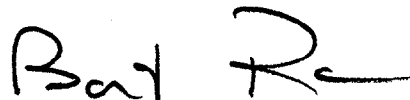
Dockets Management Branch  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane  
Rockville, MD 20852

**Re: Docket No.: 99P-5215CP**

Dear Madam or Sir:

Enclosed please find a copy of a letter that we have submitted in the docket for a Petition recently filed by Faulding Pharmaceutical Co. ("Faulding") (Docket No. 99P-2252CPI), which concerns FDA's enforcement of the Pediatric Rule, challenged in our Citizen Petition (Docket No. 99P-5215CP). Because Faulding's Petition presents in a very stark way certain of the problems with enforcing the Pediatric Rule that we predicted would occur, we have requested that FDA consolidate Faulding's Petition with our Petition as FDA reconsiders the Pediatric Rule. We believe that careful reevaluation of the Pediatric Rule in light of the two Petitions will demonstrate that (1) the Rule was an ill-conceived and legally impermissible set of regulations that is already beginning to cause the collateral problems about which we warned in our Citizen Petition, and (2) for the reasons stated in the two Petitions, it should therefore be revoked.

Respectfully submitted,



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99P-5215

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Docket No. 99P-5215CP  
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March 1, 2000

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Food and Drug Administration  
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**Re: Docket No.: 99P-2252CPI**

Dear Madam or Sir:

The undersigned has become aware that Faulding Pharmaceutical Co. ("Faulding") is seeking relief from the application of the Pediatric Rule to its suitability petition for a new dosage form of Pamidromate Disodium Injection. As stated in our Citizen Petition requesting that the Commissioner revoke the Pediatric Rule, we believe that any application of that rule which restricts the choices available to consumers is unlawful and inappropriate. See Dec. 2, 1999 letter from Daniel Troy to FDA (Docket No. 99P-5215CP) (Exh. 1 hereto). We understand why established principles of administrative law require FDA to apply the Pediatric Rule to Faulding – and indeed to all ANDA applicants – but we find the consequences of that administrative consistency unacceptable. For that reason, and because Faulding's request highlights a problem anticipated in our Petition, we respectfully urge FDA to consolidate Faulding's Petition (Docket No. 99P-2252CPI) and our Petition (Docket No. 99P-5215CP). We believe that a consolidated review of the two Petitions will establish that FDA cannot implement the Pediatric Rule without either (1) thwarting other key aspects of the drug approval process by enforcing the Rule consistently, or (2) acting in an arbitrary and capricious manner with respect to the products for which FDA requires pediatric testing. Because either of these results is unsustainable, FDA should revoke the Pediatric Rule for the reasons stated in our Petition.

Faulding's complaint concerns FDA's refusal to approve its suitability petition for Pamidronate Disodium, which it intends to market pursuant to the Abbreviated New Drug Application ("ANDA") process based on the reference listed pioneer drug Aredia, manufactured by Novartis Pharmaceuticals Corporation. Specifically, FDA has required Faulding to test its proposed drug for safety and effectiveness in pediatric populations – even though

- (1) the pioneer drug upon which the application is based is not labeled for use in pediatric populations; and
- (2) the only change between the pioneer drug and Faulding's generic version was a slight variation in dosage forms that Faulding claims has no effect

on the product's safety or effectiveness in pediatric populations vis-a-vis the pioneer product.<sup>1</sup>

See Oct. 22, 1999 letter from Douglas L. Sporn to Kala Patel (Docket No. 99P-2252CPI). Faulding urges FDA not to apply the Pediatric Rule to suitability petitions, which, like Faulding's Petition, are routinely filed for changes in dosage form that may have nothing to do with a product's relative safety and effectiveness in pediatric populations. See Nov. 16, 1999 letter from Heike Maaser to Douglas L. Sporn, at 1-2 (Docket No. 99P-2252CPI); Oct. 7, 1999 letter from Robert A. Dormer to Janet Woodcock, at 6 (Docket No. 99P-2252CPI).

The erroneous "intended use" theory underlying FDA's new Pediatric Rule compels FDA's refusal to approve Faulding's suitability petition so that FDA can avoid acting in an arbitrary or capricious manner. In contrast to its historical regulation of only those uses of a drug that the manufacturer claims in the product's labeling, FDA has taken the position in promulgating the Pediatric Rule that it also may regulate merely foreseeable uses – pediatric uses in particular – of a product.<sup>2</sup> Because Faulding seeks approval of a product that, like Aredia itself, apparently treats conditions that occur in pediatric populations, FDA has disabled itself from exempting Faulding from FDA's regulation of these foreseeable, but unclaimed, uses of its product.

As a matter of administrative law, to maintain consistent application of the Pediatric Rule, FDA's regulations must go even further. FDA also would be legally required to refuse to approve ANDAs for identical generic copies (*i.e.*, pharmaceutical equivalents) of Aredia.<sup>3</sup>

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<sup>1</sup> Although Aredia is marketed in powder form and must be reconstituted into a solution prior to injection, Pamidronate Disodium will be sold in a ready-to-use injectable solution. See Oct. 7, 1999 letter from Robert A. Dormer to Janet Woodcock, at 2 (Docket No. 99P-2252CPI).

<sup>2</sup> See Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients: Final Rule, 63 Fed. Reg. 66,632, 66,657-58 (1998) (asserting that "[i]ntended uses" encompass more than the uses explicitly included in the manufacturer's proposed labeling" but also include "actual uses of the drug of which the manufacturer has, or should have, notice, even if those uses are not promoted by the manufacturer"); *id.* at 66,645 ("Pediatric patients are a significant subpopulation, affected by many of the same diseases as adults, and are foreseeable users of new drugs and biologics." (emphasis added)).

<sup>3</sup> For that matter, FDA logically would be required to find Aredia itself, which also has not been established to be safe and effective for use in pediatric populations, to be misbranded. Because Aredia was approved before the effective date of the Pediatric Rule, however, we recognize that FDA may invoke "enforcement discretion" to refuse to take action  
(Continued...)

Because the generic copy of Aredia foreseeably could be used in pediatric populations, pediatric use is an "intended use" of the drug that must be established to be safe and effective before the product can be legally marketed, under FDA's theory. Pediatric use of that product would not have been established to be safe and effective, however, as Aredia itself, upon which the ANDA would be based, was never established to be safe and effective for pediatric use.

FDA has placed itself in a position where approval of an ANDA based on Aredia without pediatric testing would trigger two legal violations under FDA's "intended use" theory. First, FDA would be authorizing the distribution of a product that has not been established to be safe and effective for each of its intended uses, which, in FDA's view, include pediatric uses. See Brief for FDA at 31, Washington Legal Found. v. Henney, 2000 WL 122099, No. 99-5304 (D.C. Cir. Feb. 11, 2000) (asserting that "if the manufacturer has not demonstrated that the intended use of the product is safe and effective, the manufacturer's continued introduction of the product into interstate commerce is unlawful" as long as the use remains an "intended use") (Exh. 2 hereto). Second, FDA would be authorizing the illegal distribution of a "misbranded" product because the drug's label would not contain adequate directions for pediatric use. See Reply Brief for FDA at 6, Washington Legal Found. v. Henney, 2000 WL 122099, No. 99-5304 (D.C. Cir. Feb. 11, 2000) ("If the labeling does not indicate all intended uses, the product is misbranded, and its interstate distribution is unlawful.") (Exh. 3 hereto).<sup>4</sup> Thus, FDA, having created the Pediatric Rule on a faulty legal and policy premise, must now enforce it across the board with respect to new drugs, identical generic copies of approved pioneer drugs, and slight variations of approved pioneer drugs for which a suitability petition is required.

FDA apparently recognizes the damage that a consistent application of the Pediatric Rule may cause. FDA thus does not intend to enforce the Pediatric Rule with respect to ANDAs for generic pharmaceutical equivalents<sup>5</sup> although it does intend to enforce the Rule for most

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(...Continued)

against Aredia under the Pediatric Rule. See Heckler v. Chaney, 470 U.S. 821, 831-32 (1985).

<sup>4</sup> See also 21 U.S.C. § 352(f) (1994) (providing that product not bearing adequate directions for use is misbranded); 21 C.F.R. § 201.100 (1999) (defining "adequate directions for use" for prescription drugs to mean directions sufficient to enable a medical professional to administer the drug for each intended use); id. § 201.5 (defining "adequate directions for use" for nonprescription drugs to mean "directions under which the layman can use a drug safely and for the purposes for which it is intended" (emphasis added)); 21 U.S.C. § 331(a) (prohibiting introduction into interstate commerce of misbranded product). FDA cannot excuse these actions as acts of "enforcement discretion" because they involve mandatory decisions, not allocations of limited enforcement resources.

<sup>5</sup> See 63 Fed. Reg. at 66,640 ("This rule does not impose any requirements on studies submitted in support of applications for generic copies of approved drugs that meet the

(Continued...)

suitability petitions, as Faulding's petition confirms. FDA's selective enforcement of the Pediatric Rule to generic drugs based on whether a suitability petition is required is misguided and nonsensical. Congress intended that the only permissible ground for denying a suitability petition is if the change itself from the pioneer drug to the generic version adversely affected the safety or efficacy of the drug.<sup>6</sup> In most cases, the changes to a generic drug that require the filing of a suitability petition have no effect on the product's safety or effectiveness in pediatric populations, as the current case may illustrate. If the only difference between Faulding's product and Aredia is that Faulding's product is to be sold as a pre-made solution ready for injection, while Aredia itself would be sold in powder form to be reconstituted into a solution prior to injection, then the patient will receive an injection either way. There is nothing inherent in this minor variation in dosage form that would make pediatric uses more or less risky or more or less likely with respect to Faulding's product, as opposed to Aredia itself. In short, FDA's reliance upon the filing of a suitability petition as a basis for enforcing the Pediatric Rule against Faulding, although reaching a legally correct result, is itself arbitrary and capricious.

Indeed, it appears that the line FDA has drawn for determining whether to enforce the Pediatric Rule is even more arbitrary and capricious than the Faulding case alone reveals. FDA has threatened to enforce the Pediatric Rule with respect to suitability petitions for "a change in active ingredient, dosage form, or route of administration" but has issued no such enforcement threat for suitability petitions for a change in dosage strength. See Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule, 63 Fed. Reg. 66,632, 66,640-41 (1998). In other words, FDA's current enforcement position is apparently

1. to enforce the Rule for New Drug Applications and suitability petitions for "a change in active ingredient, dosage form, or route of administration," but
2. not to enforce the Rule for ANDAs for generic pharmaceutical equivalents and suitability petitions for a change in dosage strength.

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(...Continued)

requirements of section 505(j) of the act.").

<sup>6</sup> See H.R. Rep. No. 98-857, pt. 1, at 23 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2656 ("The FDA must approve a petition to submit an ANDA for a differing generic drug unless clinical studies are needed to show the safety and effectiveness of the change." (emphasis added)) (Exh. 4 hereto); 21 U.S.C. § 355(j)(2)(A)(iii) (1994 & Supp. III 1997) (authorizing FDA to require additional information for suitability petition respecting the route of administration, dosage form, or strength with respect to which the [suitability] petition was filed" (emphasis added)); Oct. 7, 1999 letter from Robert A. Dormer to Janet Woodcock, at 3 (Docket No. 99P-2252CPI).

There is no reasoned basis for this distinction – according to FDA’s theory, if the proposed drug treats a condition occurring in pediatric populations, pediatric testing legally should be required in all of the above-listed instances. FDA’s decision to apply the Pediatric Rule selectively based on the above-stated criteria illustrates the bankruptcy of the theory that underlies the Pediatric Rule itself.

Our Petition argued that, in addition to the legal problems arising from the Pediatric Rule, the Rule represents bad policy. FDA’s dilemma in the Faulding matter confirms that point. Specifically, the Pediatric Rule will force FDA to make a Hobson’s choice between two unhappy alternatives. First, FDA could consistently apply the Rule to all new drugs that foreseeably could be used in pediatric populations. This approach, however, could hamper the ANDA approval process, which was designed to promote competition by ensuring approval – without the need for additional testing – of low-cost generic drugs that were bioequivalent to, and labeled for the same conditions of use as, an approved pioneer drug.<sup>7</sup> Instead of this streamlined approval process, consistent application of the Rule would hinder that process by requiring FDA to deny approval of ANDAs based upon pioneer drugs that were not approved for pediatric use until pediatric testing is conducted. See Dec. 2, 1999 letter from Daniel Troy to FDA, App. B, at B-16 to B-17 (Docket No. 99P-5215CP) (Exh. 1 hereto).

Second, FDA could try to enforce the Rule against ANDA applicants selectively, based on some other irrelevant decisional criterion such as suitability petitions, as it has apparently decided to do. This approach, however, has placed FDA in an arbitrary and capricious position with respect to the ANDA products and suitability petitions for which it requires no pediatric testing.

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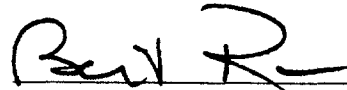
<sup>7</sup> See 21 U.S.C. § 355(j)(2)(A)(i), (iv), (v), (4)(B), (F), (G); Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1068 (D.C. Cir. 1998) (observing that “Congress’s central goal, in enacting the Hatch-Waxman Amendments, [was] to bring generic drugs onto the market as rapidly as possible”) (emphasis added)); H.R. Rep. No. 98-857, pt. 1, at 21, 1984 U.S.C.C.A.N. at 2654 (“[A]n ANDA may not be considered for a condition of use that has not previously been approved for the listed drug.”) (Exh. 4 hereto); id. at 14, 1984 U.S.C.C.A.N. at 2647 (observing that goal of ANDA process is “to make available more low cost generic drugs”) (Exh. 4 hereto).

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*Wiley, Rein & Fielding*

The proper escape from this conundrum is for FDA to revoke the Pediatric Rule and revert to its historical practice of regulating only those drug uses that are claimed in a product's labeling. Because Faulding's Petition confirms the predictions made in our Citizen Petition, we respectfully request that FDA consolidate the two Petitions. We believe that careful reevaluation of the Pediatric Rule in light of the two Petitions will demonstrate that (1) it was an ill-conceived and legally impermissible set of regulations that is already beginning to cause the problems about which we warned in our Citizen Petition, and (2) for the reasons stated in the two Petitions, it should therefore be revoked.

Respectfully submitted,



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December 2, 1999

Dockets Management Branch  
Food and Drug Administration  
Department of Health and Human Services  
Room 1-23  
12420 Parklawn Drive  
Rockville, MD 20857

## **CITIZEN PETITION**

The undersigned, on behalf of the American Association of Physicians and Surgeons, the Competitive Enterprise Institute, and Consumer Alert, submits this petition under sections 201(n) and (p), 301(a) and (d), 502(a), (f), and (j), 505(a), (d)(7), (i), and (k), and 701(a) of the Federal Food, Drug, and Cosmetic Act and section 351 of the Public Health Service Act to request the Commissioner of Food and Drugs to revoke FDA's regulations concerning pediatric testing of drugs, as published at 63 Fed. Reg. 66,632 (1998), and to refrain from taking any form of administrative action pursuant to those rules.

### **A. Action requested**

The Commissioner should immediately revoke the following provisions of Title 21 of the Code of Federal Regulations:

#### **PART 201 - LABELING**

##### **Sec. 201.23 Required pediatric studies.**

(a) A manufacturer of a marketed drug product, including a biological drug product, that is used in a substantial number of pediatric patients, or that provides a meaningful therapeutic benefit over existing treatments for pediatric patients, as defined in Secs. 314.55(c)(5) and 601.27(c)(5) of this chapter, but whose label does not provide adequate information to support its safe and effective use in pediatric populations for the approved indications may be required to submit an application containing data adequate to assess whether the drug product is safe and effective in pediatric populations. The application may be required to contain adequate evidence to support dosage and administration in some or all pediatric subpopulations, including neonates, infants, children, and adolescents, depending upon the known or appropriate use of the drug product in such subpopulations. The applicant may also be required to develop a pediatric formulation for a drug product that represents a meaningful therapeutic benefit over existing therapies for



pediatric populations for whom a pediatric formulation is necessary, unless the manufacturer demonstrates that reasonable attempts to produce a pediatric formulation have failed.

(b) The Food and Drug Administration (FDA) may by order, in the form of a letter, after notifying the manufacturer of its intent to require an assessment of pediatric safety and effectiveness of a pediatric formulation, and after offering an opportunity for a written response and a meeting, which may include an advisory committee meeting, require a manufacturer to submit an application containing the information or request for approval of a pediatric formulation described in paragraph (a) of this section within a time specified in the order, if FDA finds that:

(1) The drug product is used in a substantial number of pediatric patients for the labeled indications and the absence of adequate labeling could pose significant risks to pediatric patients; or

(2) There is reason to believe that the drug product would represent a meaningful therapeutic benefit over existing treatments for pediatric patients for one or more of the claimed indications, and the absence of adequate labeling could pose significant risks to pediatric patients.

(c)(1) An applicant may request a full waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed, or

(ii) There is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups.

(2) An applicant may request a partial waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The product:

(A) Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, and

(B) Is not likely to be used in a substantial number of patients in that age group, and

(C) The absence of adequate labeling could not pose significant risks to pediatric patients; or

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed, or

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in that age group, or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(3) FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the

grounds for waiver specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(d) If a manufacturer fails to submit a supplemental application containing the information or request for approval of a pediatric formulation described in paragraph (a) of this section within the time specified by FDA, the drug product may be considered misbranded or an unapproved new drug or unlicensed biologic.

## **PART 312 – INVESTIGATIONAL NEW DRUG APPLICATION**

### **Sec. 312.23 IND content and format.**

(a) \* \* \*

(10) \* \* \*

(iii) Pediatric studies. Plans for assessing pediatric safety and effectiveness.

\* \* \* \* \*

### **Sec. 312.47 Meetings.**

\* \* \* \* \*

(b) \* \* \*

(1) End-of-Phase 2 meetings – (i) Purpose. The purpose of an end-of-phase 2 meeting is to determine the safety of proceeding to Phase 3, to evaluate the Phase 3 plan and protocols and the adequacy of current studies and plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

\* \* \* \* \*

(iv) Advance information. At least 1 month in advance of an end-of-Phase 2 meeting, the sponsor should submit background information on the sponsor's plan for Phase 3, including summaries of the Phase 1 and 2 investigations, the specific protocols for Phase 3 clinical studies, plans for any additional nonclinical studies, plans for pediatric studies, including a time line for protocol finalization, enrollment, completion, and data analysis, or information to support any planned request for waiver or deferral of pediatric studies, and, if available, tentative labeling for the drug. \* \* \*

(v) Conduct of meeting. \* \* \* The adequacy of the technical information to support Phase 3 studies and/or a marketing application may also be discussed. FDA will also provide its best judgment, at that time, of the pediatric studies that will be required for the drug product and whether their submission will be deferred until after approval. \* \* \*

(2) "Pre-NDA" and "pre-BLA" meetings. \* \* \* The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those

studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to identify the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application. \* \* \*

To permit FDA to provide the sponsor with the most useful advice on preparing a marketing application, the sponsor should submit to FDA's reviewing division at least 1 month in advance of the meeting the following information:

\* \* \* \* \*

(iii) Information on the status of needed or ongoing pediatric studies.

\* \* \* \* \*

Sec. 312.82 Early consultation.

\* \* \* \* \*

(a) Pre-investigational new drug (IND) meetings. \* \* \* The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.

(b) End-of-phase 1 meetings. \* \* \* The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the drug in pediatric patients. For drugs for life-threatening diseases, FDA will provide its best judgment, at that time, whether pediatric studies will be required and whether their submission will be deferred until after approval. \* \* \*

**PART 314 – APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG**

Sec. 314.50 Content and format of an application.

\* \* \* \* \*

(d) \* \* \*

(7) Pediatric use section. A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under Sec. 314.55.

\* \* \* \* \*

Sec. 314.55 Pediatric use information.

(a) Required assessment. Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Assessments of safety and effectiveness required under this section for a drug product that represents a meaningful therapeutic benefit over existing treatments for pediatric patients must be carried out using appropriate formulations for each age group(s) for which the assessment is required.

(b) Deferred submission. (1) FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (a) of this section until after approval of the drug product for use in adults. Deferral may be granted if, among other reasons, the drug is ready for approval in adults before studies in pediatric patients are complete, or pediatric studies should be delayed until additional safety or effectiveness data have been collected. If an applicant requests deferred submission, the request must provide a certification from the applicant of the grounds for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time.

(2) If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the drug product may be approved for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(c) Waivers – (1) General. FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant. A request for a waiver must provide an adequate justification.

(2) Full waiver. An applicant may request a waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

(3) Partial waiver. An applicant may request a waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed;

(iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) FDA action on waiver. FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(5) Definition of "meaningful therapeutic benefit". For purposes of this section and Sec. 201.23 of this chapter, a drug will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that:

(i) If approved, the drug would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population. Examples of how improvement might be demonstrated include, for example, evidence of increased effectiveness in treatment, prevention, or diagnosis of disease, elimination or substantial reduction of a treatment-limiting drug reaction, documented enhancement of compliance, or evidence of safety and effectiveness in a new subpopulation; or

(ii) The drug is in a class of drugs or for an indication for which there is a need for additional therapeutic options.

(d) Exemption for orphan drugs. This section does not apply to any drug for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.

Sec. 314.81 Other postmarketing reports.

\* \* \* \* \*

(b) \* \* \*

(2) \* \* \*

(i) Summary. A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study. The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form. \* \* \* \* \*

(vi) \* \* \*

(c) Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(vii) Status reports. A statement on the current status of any postmarketing studies performed by, or on behalf of, the applicant. The statement shall include whether postmarketing clinical studies in pediatric populations were required or agreed to, and if so, the status of these studies, e.g., to be initiated, ongoing (with projected completion date), completed (including date), completed and results submitted to the NDA (including date). To facilitate communications between FDA and the applicant, the report may, at the applicant's discretion, also contain a list of any open regulatory business with FDA concerning the drug product subject to the application. \* \* \* \* \*

**PART 601 – LICENSING**

Sec. 601.27 Pediatric studies.

(a) Required assessment. Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Where the course of the disease and the effects of the product are similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled effectiveness studies in adults, usually supplemented with other information in pediatric

patients, such as pharmacokinetic studies. In addition, studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Assessments required under this section for a product that represents a meaningful therapeutic benefit over existing treatments must be carried out using appropriate formulations for the age group(s) for which the assessment is required.

(b) **Deferred submission.** (1) FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (a) of this section until after licensing of the product for use in adults. Deferral may be granted if, among other reasons, the product is ready for approval in adults before studies in pediatric patients are complete, pediatric studies should be delayed until additional safety or effectiveness data have been collected. If an applicant requests deferred submission, the request must provide an adequate justification for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time.

(2) If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the product may be licensed for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(c) **Waivers – (1) General.** FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant. A request for a waiver must provide an adequate justification.

(2) **Full waiver.** An applicant may request a waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups.

(3) **Partial waiver.** An applicant may request a waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed;

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) FDA action on waiver. FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(5) Definition of "meaningful therapeutic benefit". For purposes of this section, a product will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that:

(i) If approved, the product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population. Examples of how improvement might be demonstrated include, e.g., evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; elimination or substantial reduction of a treatment-limiting drug reaction; documented enhancement of compliance; or evidence of safety and effectiveness in a new subpopulation; or

(ii) The product is in a class of products or for an indication for which there is a need for additional therapeutic options.

(d) Exemption for orphan drugs. This section does not apply to any product for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.

#### Sec. 601.37 Annual reports of postmarketing pediatric studies.

Sponsors of licensed biological products shall submit the following information each year within 60 days of the anniversary date of approval of the license, to the Director, Center for Biologics Evaluation and Research:

(a) Summary. A brief summary stating whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

(b) Clinical data. Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An



assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(c) Status reports. A statement on the current status of any postmarketing studies in the pediatric population performed by, or on behalf of, the applicant. The statement shall include whether postmarketing clinical studies in pediatric populations were required or agreed to, and if so, the status of these studies, e.g., to be initiated, ongoing (with projected completion date), completed (including date), completed and results submitted to the BLA (including date).

## **B. Statement Of Grounds For Revoking The Pediatric Rule**

### **1. Petitioners**

The Association of American Physicians and Surgeons ("AAPS") is a not-for-profit membership organization that represents approximately 4,000 physicians nationwide in all practices and specialties. It was established in 1943 to preserve the practice of private medicine, and has remained dedicated to the Oath of Hippocrates and the sanctity of the patient-physician relationship, which AAPS believes must be protected from all forms of third-party intervention. Indeed, since its founding over fifty years ago, AAPS has been the only national organization consistently supporting free market principles in medical practice. AAPS seeks reconsideration of FDA's Pediatric Rule on the ground that it impedes the ability of physicians to treat their patients by diminishing the choices available to prescribing physicians. AAPS believes that FDA should not direct the research efforts of pharmaceutical companies. Rather, it should expeditiously approve all drugs that are safe and effective for the purposes for which they are intended, and leave to doctors, in consultation with their patients, the decision of whether any "off-label" use is appropriate.<sup>1</sup>

The Competitive Enterprise Institute ("CEI") is a non-profit public policy organization dedicated to the principles of free enterprise and limited government. CEI believes that consumers are best helped by being allowed to make their own choices in a free marketplace, rather than by being forced into decisions because of government regulation. CEI is nationally recognized as a leading voice on a broad range of regulatory issues ranging from environmental laws to antitrust policy to regulatory risk. CEI reaches out to the public and the media to ensure that its ideas are heard, works with policymakers to ensure that they are implemented, and, when

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<sup>1</sup> Use of a product for a purpose or in a manner not suggested by the product's labeling constitutes an "off-label use." "Off-label uses include treating a condition not indicated on the label, or treating the indicated condition but varying the dosing regimen or the patient population" from that indicated on the label. Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 55 (D.D.C. 1998), appeal docketed, No. 99-5304 (D.C. Cir. Sept. 9, 1999).

necessary, takes its arguments to court to ensure that the law is upheld. CEI objects to FDA's unprecedented assertion of authority to order manufacturers to conduct studies with respect to uses that they do not intend to claim on their labels or otherwise promote. CEI particularly objects to FDA's claim that it can direct a drug company to reformulate a drug if FDA believes that such a reformulation may have a beneficial pediatric use. Such an approach is not only inefficient, but will dramatically raise the costs and diminish the availability of drugs to consumers.

Consumer Alert is a national, non-profit, non-partisan membership organization for people concerned about the excessive growth of government regulation at the national and state levels. Founded in 1977, Consumer Alert is dedicated to informing the public about the consumer benefits of competitive enterprise and to promoting sound economic, scientific, and risk data in public policy decisions. Consumer Alert's vision of consumerism is that advancing competition is the best regulator of business, and that individual choice is the best expression of consumer interest. Consumer Alert's mission is to enhance understanding and appreciation of the consumer benefits of a market economy so that individuals and policymakers rely more on private, rather than governmental, approaches to consumer concerns. Like CEI, Consumer Alert objects to the Pediatric Rule as an unnecessary and unwarranted governmental intrusion into what should essentially be private manufacturer decisions concerning which drug uses to study and obtain FDA approval to market and which formulations to develop.

On behalf of the doctors, patients, and drug manufacturers who are members of the petitioning organizations, AAPS, CEI, and Consumer Alert ("Petitioners") hereby request that FDA reconsider and withdraw its Pediatric Rule for the following reasons:

- First, the Pediatric Rule conflicts with the pediatric exclusivity provision in the Food and Drug Administration Modernization and Accountability Act of 1997 ("FDAMA"), Pub. L. No. 105-115, 111 Stat. 2296 (1997), that Congress established to encourage voluntary pediatric testing. Since FDA published its Final Rule, actual experience has demonstrated that this mechanism is working well, rendering the Pediatric Rule unnecessary. See App. A., pp. A-1 to A-26.
- Second, the Pediatric Rule conflicts with FDAMA's goal of streamlining the drug approval process by instead increasing the cost of pharmaceuticals, further delaying the introduction of new drugs to market, and hampering new drug innovation. See App. A, pp. A-26 to A-39.
- Third, FDA's decision to characterize pediatric uses as foreseeable and therefore "intended" so that FDA can then compel either pediatric clinical studies or possibly the development of pediatric formulations is a dramatic, unprecedented, and illegal assertion of authority, see App. B, for which FDA has supplied no satisfactory justification, see App. C.

- Finally, as a matter of sound public policy and basic constitutional principles, the Pediatric Rule – which forces manufacturers to conduct expensive clinical research and to reformulate a safe and effective product to sell to persons to whom they do not intend to sell – represents an unnecessary intrusion into manufacturers' basic decisional prerogatives concerning the intended purchasers of its products and a prime example of regulatory overreaching. See App. D.

Although Petitioners did not participate in the rulemaking, the adverse impact of this Rule on their members warrants the action requested in this Petition.<sup>2</sup> Moreover, although FDA may have considered some of the arguments made below in the course of the rulemaking, FDA has failed to justify its unprecedented assertion of authority to (1) deem certain uses "foreseeable" – even for drugs that have not yet actually been sold, and even if the manufacturer disclaims those uses – and (2) treat those allegedly "foreseeable" uses as "intended uses" for which manufacturers must conduct and submit testing information establishing the safety and effectiveness of the drugs.<sup>3</sup> FDA's failure to articulate a theory justifying its assertion of power to direct manufacturers to engage in research to prove the safety and effectiveness even of disclaimed uses, as well as the new evidence confirming the effectiveness of the incentive-based provisions of FDAMA, warrant a thorough reconsideration, and revocation, of the Pediatric Rule.

## 2. Description of the Pediatric Rule

Without demonstrating the existence of any problem warranting government intervention or providing an adequate legal foundation, FDA has established an extensive layer of regulations forcing manufacturers to seek approval for use on pediatric populations of drugs that are labeled and promoted only for adults. Specifically, with respect to "each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration," the Pediatric Rule requires manufacturers to submit "data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric

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<sup>2</sup> Courts have "found injury-in-fact where the defendants' actions impaired the plaintiffs' access to certain goods." Arent v. Shalala, 866 F. Supp. 6, 10 (D.D.C. 1994) (citing Competitive Enter. Inst. v. NHTSA, 901 F.2d 107, 113 (D.C. Cir. 1990)), aff'd in part and remanded in part on other grounds, 70 F.3d 610 (D.C. Cir. 1995). In Arent, the court also found that even "where the plaintiff is not itself the subject of the contested regulatory action," it still may be within the "zone of interests" if it is directly interested as a purchaser of the regulated product. 866 F. Supp. at 12. As physicians whose ability to treat patients will be compromised by the delays and increased costs that the Pediatric Rule will cause, and as representatives of patients whose health will be compromised, Petitioners plainly fall into this "zone of interests."

<sup>3</sup> For an explanation of the term "intended use," see App. B, p. B-1.

subpopulation for which the drug is safe and effective.” 21 C.F.R. § 314.55(a) (1999).<sup>4</sup> The Rule further requires manufacturers to develop and use pediatric formulations appropriate for each age group in which the clinical studies needed to generate the requisite data of safety and effectiveness are conducted. See id.

The Rule permits deferral of these requirements – at FDA’s discretion – to expedite the drug approval process or to address safety concerns with testing the drug on children before its safety and/or effectiveness in adults has been adequately established. See id. § 314.55(b). Similarly, the Rule permits waiver of these requirements if:

- (i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;
- (ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or
- (iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

Id. § 314.55(c).

The Rule does not, however, permit waiver or deferral of these requirements based on a manufacturer’s certification that it does not intend to market the drug for pediatric use. See id. § 314.55. Thus, whereas manufacturers once could control the uses for which they conducted clinical studies and sought approval of new drug products, FDA has now forced manufacturers to conduct studies and develop formulations for uses of a new drug that manufacturers may not desire to pursue.<sup>5</sup>

With respect to marketed drugs that have not been approved for pediatric use, the Rule purports to allow FDA to require manufacturers to “submit an application containing data adequate to assess whether the drug product is safe and effective in pediatric populations.” Id. § 201.23(a) (1999). This includes, at FDA’s discretion, “adequate evidence to support dosage and administration in some or all pediatric subpopulations.” Id. The Rule also purports to allow FDA to require manufacturers “to develop a pediatric formulation for a drug product that

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<sup>4</sup> All emphasis in this letter and the accompanying appendices is added unless otherwise noted.

<sup>5</sup> Indeed, FDA has long required manufacturers to disclaim pediatric uses in the absence of clinical testing. See 21 C.F.R. § 201.57(f)(9)(v), (vi) (1999).

represents a meaningful therapeutic benefit over existing therapies for pediatric populations for whom a pediatric formulation is necessary, unless the manufacturer demonstrates that reasonable attempts to produce a pediatric formulation have failed." Id.

Although the regulation concerning marketed drugs contains waiver provisions similar to those governing new drugs, a manufacturer cannot obtain a waiver merely because it does not wish to expand the uses of its product to pediatric populations. See id. § 201.23(c). If a manufacturer does not comply with FDA's pediatric testing requirement, FDA asserts the authority to declare the offending product to be "misbranded or an unapproved new drug or unlicensed biologic." Id. § 201.23(d); 21 U.S.C. § 355(d) (1994 & Supp. III 1997).<sup>6</sup> FDA claims this authority notwithstanding its necessary previous finding that precisely the same product is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." 21 C.F.R. § 201.23(d); 21 U.S.C. § 355(d).

### 3. Summary of Argument

FDA should immediately revoke the regulations comprising the Pediatric Rule. The Pediatric Rule is fundamentally inconsistent with key purposes and provisions of FDAMA which encourage manufacturers to bring off-label uses on-label voluntarily – that is, in response to incentives rather than by FDA fiat. One of these incentives encourages manufacturers to seek approval for use of their drugs in pediatric populations by offering them an additional six months of exclusivity for their drugs under certain circumstances. 21 U.S.C. § 355a (Supp. III 1997). Another important FDAMA provision requires FDA to publish "standards for the prompt review of supplemental applications" to encourage manufacturers to seek approval for off-label uses of marketed drugs. See 21 U.S.C. § 371 note (Supp. III 1997). The Pediatric Rule, however, requires precisely the same type of studies that the statute only authorizes FDA to request. The mandatory nature of the Pediatric Rule also creates serious ethical problems associated with drug testing on children that are minimized under Congress's voluntary scheme. For a more detailed discussion of these points, see App. A, pp. A-2 to A-26.

The Pediatric Rule also conflicts with FDAMA's goal of reducing the inordinate amount of time that FDA consumes in approving new drug applications ("NDAs"). To effectuate this purpose, Congress included provisions in FDAMA designed to: (1) abbreviate and simplify the data necessary for FDA to conclude that a drug is safe and effective, 21 U.S.C. § 355(d); (2) streamline clinical research on drugs, id. § 355(i); and (3) institute a fast-track approval process for drugs to treat life-threatening illnesses, id. § 356. Yet the Pediatric Rule requires not only

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<sup>6</sup> In the vast majority of cases, however, FDA does not actually intend to seize the offending drugs and remove them from the market as provided in 21 U.S.C. § 334 (1994 & Supp. III 1997). Rather, FDA intends to seek court injunctions requiring manufacturers to conduct the testing required by the Pediatric Rule. See 63 Fed. Reg. at 66,655.

additional clinical studies but also the potential development of pediatric formulations of certain drugs. Thus, the Rule will render the already cumbersome drug approval process costlier, slower, and even more inefficient. For a more detailed discussion of this point, see App. A, pp. A-26 to A-39.

In addition to conflicting with key FDAMA goals, the Pediatric Rule contravenes the long-standing and universal understanding of Congress, the courts, and FDA concerning the nature of the "intended uses" of drug products that are subject to FDA's regulatory authority. From the 1906 inception of national food and drug law to the present, drug manufacturers have always determined the "intended uses" for which they sought approval to market their drug products by virtue of the promotional claims they made in their product's labeling. Any other uses – no matter how foreseeable or desired – were considered to be "off-label" and, thus, outside of FDA's jurisdiction.

FDA's promulgation of the Pediatric Rule, by contrast, would overturn this long-standing and universally understood balance of power by purporting to allow FDA – rather than the manufacturer – to determine the uses to which the manufacturer's product would be put. Specifically, FDA has asserted the right to require manufacturers of both new and marketed drugs to seek approval for use of their drugs on pediatric populations – even though the manufacturer may only desire to market its drug to adult populations. See 21 C.F.R. §§ 201.23, 314.55. Under the Pediatric Rule, FDA may now even force a manufacturer to develop new formulations of a drug for uses for which the manufacturer never intended to seek approval. See 21 C.F.R. §§ 201.23, 314.55. Not only has FDA far exceeded its congressional mandate in treating foreseeable uses as "intended uses," but it has also gone farther afield by creating a per se presumption that certain uses are foreseeable even where (1) the drug has not actually been marketed, and (2) the manufacturer has affirmatively disclaimed the allegedly "foreseeable" use at issue. FDA should immediately cease such unwarranted intrusion into determining the uses for which drugs will be marketed, which Congress historically has made the manufacturers' exclusive province. For a more detailed discussion of these points, see App. B, pp. B-1 to B-15.

If taken to its logical conclusion, the theory underlying the Pediatric Rule would render the drug approval and misbranding mechanisms of the Food, Drug, and Cosmetic Act ("FDCA"), Pub. L. No. 75-717, 52 Stat. 1040 (1938), virtually inoperable. For example, requiring manufacturers to conduct clinical studies to establish the safety and efficacy of all arguably foreseeable uses of each new drug that they seek to market would dramatically delay the necessary approvals for marketing those drugs. Moreover, the "Abbreviated New Drug Application" ("ANDA") process for generic follow-on drugs – which requires the ANDA to contain substantially identical labeling to the pioneer label – would cease to function if ANDA applicants were required to claim, on their labeling, foreseeable uses that were unforeseen when the pioneer drug's label was approved. Further, considering foreseeable uses to be "intended" would render the overwhelming majority of marketed drugs "misbranded" because their labels would not contain adequate directions for each "intended use" of the drug as required by law. See 21 U.S.C. § 352 (1994 & Supp. III 1997); 21 C.F.R. §§ 201.5, 201.100 (1999). FDA cannot

avoid these harsh consequences by selectively enforcing its newly created foreseeability theory, which would be impermissible in any event. For a more detailed discussion of these points, see App. B, pp. B-15 to B-22. Thus, FDA's per se "foreseeability" theory, and consequently the Pediatric Rule, are untenable.

In addition to conflicting with key purposes of FDAMA and flying in the face of well-settled understanding of the types of intended uses subject to FDA's regulatory authority, the Pediatric Rule finds no statutory support in any other provision of the food and drug laws. Indeed, none of the statutory bases upon which FDA relies authorize the agency to venture so far afield from its mission of ensuring that drugs are safe and effective for their labeled indications and into the realm of direct control over manufacturer research and development of formulations. For a more detailed discussion of this point, see App. D.

In sum, FDA should revoke the regulations comprising the Rule in light of:

- (1) the stark contrast between key goals of recent food and drug legislation and the Pediatric Rule's effect, see App. A;
- (2) FDA's abrogation of the well-settled "intended use" principle in purporting to dictate manufacturer decisions concerning appropriate labeled indications for their drug products, see App. B, pp. B-1 to B-15;
- (3) the disruption of Congress's drug approval and misbranding mechanisms that would ensue if FDA's per se "foreseeability" theory underlying the Rule is consistently applied, see App. B, pp. B-15 to B-22;
- (4) the lack of statutory support for the Rule, see App. C; and
- (5) the unconstitutional taking that results from enforcement of the Rule, see App. D.

#### **C. Environmental impact**

The subject matter of this petition is not within any of the categories of action for which an environmental assessment is required pursuant to 21 C.F.R. § 25.22 (1999), and is exempt pursuant to 21 C.F.R. § 25.30(h) (1999) in that it is concerned with FDA's procedures in administering the Act.

#### **D. Economic impact**

Not requested.

**E. Certification**

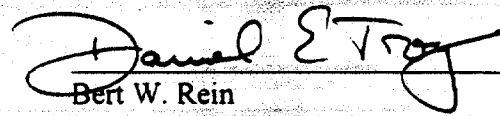
The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition, including all appendices attached hereto, includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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US OFFICE PRODUCTS

## APPENDIX A:

### THE PEDIATRIC RULE CONTRAVENES KEY PURPOSES UNDERLYING FDAMA.

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## APPENDIX A:

### **THE PEDIATRIC RULE CONTRAVENES KEY PURPOSES UNDERLYING FDAMA.**

Perhaps the most striking deficiency of the Pediatric Rule is that it clashes with fundamental policies embodied in Congress's most recent food and drug legislation, the Food and Drug Administration Modernization and Accountability Act ("FDAMA"), which was enacted barely one year before FDA promulgated the regulations comprising the Pediatric Rule. Compare Pub. L. No. 105-115, 111 Stat. 2296 (1997) with Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients: Final Rule, 63 Fed. Reg. 66,632 (1998).

It is a fundamental principle of administrative law that:

The rulemaking power granted to an administrative agency charged with the administration of a federal statute is not the power to make law. Rather, it is the power to adopt regulations to carry into effect the will of Congress as expressed by the statute.

Ernst & Ernst v. Hochfelder, 425 U.S. 185, 213-14 (1976) (internal quotations omitted). Thus,

"regulations, in order to be valid[,] must be consistent with the statute under which they are

promulgated." United States v. Larionoff, 431 U.S. 864, 873 (1977) (invalidating regulations

that were "contrary to the manifest purposes of Congress"); accord United States v. Vogel

Fertilizer Co., 455 U.S. 16, 26 (1982) ("This Court has firmly rejected the suggestion that a

regulation is to be sustained simply because it is not technically inconsistent with the statutory

language, when that regulation is fundamentally at odds with the manifest congressional design."

(internal quotations omitted)).

Far from reflecting and enforcing the congressional policies and purposes underlying FDAMA, the Pediatric Rule contravenes key FDAMA goals in at least two respects, as set forth below.

**I. THE RULE CONFLICTS WITH CONGRESS'S GOAL OF ENCOURAGING MANUFACTURERS TO BRING ADDITIONAL USES OF A DRUG ON-LABEL VOLUNTARILY.**

One major goal of FDAMA is to encourage manufacturers, through various incentive provisions, to bring off-label uses of their drugs on-label on a voluntary basis. In making these provisions voluntary rather than mandatory, Congress recognized the value of off-label uses by ensuring that cumbersome regulatory restrictions would not interfere with physicians' ability to prescribe cutting-edge medical treatments.<sup>1</sup> The Pediatric Rule, however, which requires that off-label pediatric uses be brought on-label, rejects the very notion that off-label uses represent a beneficial treatment option (as FDA has long acknowledged), and upsets Congress's carefully crafted balance concerning the appropriate circumstances for bringing off-label uses on-label.

**A. As Congress Has Recognized, Off-Label Uses Are A Common, Well-Recognized, And Essential Part Of Medical Practice.**

The label for an approved drug "identifies only those uses for which the manufacturer has conducted studies and has demonstrated, to FDA's satisfaction, substantial evidence of safety

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<sup>1</sup> Indeed, it is precisely the voluntary nature of the pediatric exclusivity provisions that is essential to keeping FDA within its statutory mandate. If manufacturers were instead required to bring off-label uses of a drug on-label, this would interfere even more with the practice of medicine than would barring physicians from prescribing drugs off-label, which is indisputably outside FDA's jurisdiction. Forbidding physicians from prescribing drugs off-label would merely eliminate certain uses of the drug. Requiring manufacturers to bring off-label uses on-label, by contrast, could cause the drug to be withdrawn from the market altogether as a "misbranded" product until the manufacturer could comply.

and effectiveness.”<sup>2</sup> Nevertheless, once “a drug or device is approved by the agency as safe and effective for one purpose, no FDA regulations prevent doctors from prescribing it for any other purpose.”<sup>3</sup> Such use is called “off-label use” and includes treating a condition not indicated on the label, or treating the indicated condition but varying the dosing regimen or the patient population.” Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 55 (D.D.C. 1998), appeal docketed, No. 99-5304 (D.C. Cir. Sept. 9, 1999).<sup>4</sup>

As FDA’s former Deputy Commissioner for Policy, William B. Schultz, has acknowledged, “FDA knows that there are important off label uses of approved drugs.”<sup>5</sup> The agency has even gone so far as to state that:

There is no FDA policy that seeks to limit physician prescribing of prescription drugs to only FDA approved indications. Such a policy would . . . be an unwarranted intrusion into the physician-patient relationship and have detrimental public health consequences. . . . We, too, recognize that the physician in clinical

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<sup>2</sup> U.S. General Accounting Office, Off-Label Drugs: Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies, Pub. No. GAO/PEMD-91-14, at 10 (1991) [hereinafter “GAO Report”].

<sup>3</sup> Michael I. Krauss, Loosening the FDA’s Drug Certification Monopoly: Implications for Tort Law and Consumer Welfare, 4 Geo. Mason L. Rev. 457, 470 (1996).

<sup>4</sup> Accord James M. Beck & Elizabeth D. Azari, FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions, 53 Food & Drug L.J. 71, 104 (1998) (describing off-label uses as “using an approved drug to treat a disease that is not indicated on its label, but is closely related to an indicated disease, treating related, unindicated diseases, and treating the indicated disease but varying from the indicated dosage, regimen, or patient population”).

<sup>5</sup> More Information for Better Patient Care: Hearing Before the Senate Comm. on Labor and Human Resources, 104th Cong. 81 (1996) (statement of William B. Schultz, FDA Dep. Comm’r for Policy); see Beck & Azari, supra note 4, at 84 (“Nothing in the FDCA . . . suggests that FDA is to conduct its own evaluations of uses other than those proposed by a manufacturer.”).

practice is well-equipped to make responsible prescribing choices for both approved and unapproved uses.<sup>6</sup>

Even this is an understatement. Off-label uses of drugs and medical devices constitute a "common and integral feature" of many, if not most, areas of medical practice.<sup>7</sup> Estimates of the number of prescriptions for off-label uses of drug products range from twenty to sixty percent of the approximately 1.6 billion prescriptions written each year.<sup>8</sup> As Michael R. Taylor, a former FDA Deputy Commissioner for Policy, has stated, "off-label use is often essential to good medical practice, and in some areas – oncology and pediatrics among them – off-label uses constitute a significant portion of standard therapy. FDA recognizes and accepts this reality."<sup>9</sup> William Hubbard, FDA's Senior Associate Commissioner for Policy, Planning, and Legislation, has likewise affirmed that "[a]ll of [FDA's] physicians and scientists . . . strongly believe in the concept of physicians being able to prescribe for off-label uses based on their own experience, knowledge, consultation with colleagues and other sources of information."<sup>10</sup>

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<sup>6</sup> Letter from Ann Witt, Acting Director of FDA Division of Drug Marketing, Advertising and Communications, Office of Drug Standards, to A. John Rush, M.D., Director, Mental Health Clinical Research Center, University of Texas at Dallas, at 1 (Jan. 17, 1991).

<sup>7</sup> Beck & Azari, supra note 4, at 79.

<sup>8</sup> See id. at 80; accord Krauss, supra note 3, at 472 (observing that twenty to sixty percent of all prescriptions written each year prescribe drugs for an off-label use).

<sup>9</sup> Michael R. Taylor, Speech of FDA Deputy Commissioner for Policy at the Food and Drug Law Institute Seminar on Drug Advertising and Promotion (Feb. 26, 1992); see Use of Approved Drugs for Unlabeled Indications, 12 FDA Drug Bulletin 4, 5 (Apr. 1982) ("'Unlabeled' uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.") [hereinafter "Unlabeled Indications"].

<sup>10</sup> Pl.'s Mem. in Supp. of Summ. J. at 9, Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51 (D.D.C. 1998) (No. 1:94CV01306) [hereinafter "WLF Mem."] (citing Hubbard Tr. 72).

In certain fields, rates of off-label use are particularly high. For example, "[o]ff-label use is common, and even predominant, in the treatment of cancer patients."<sup>11</sup> A government study that collected data from the spring of 1990 found that, of the seventeen most commonly used anti-cancer drugs, five had been used off-label at least 70% of the time.<sup>12</sup> Similarly, Carl Dixon, the President of the Kidney Cancer Association, recently stated that the "most widely prescribed medication for kidney cancer is off-label."<sup>13</sup>

Some off-label uses define "state of the art treatment."<sup>14</sup> In the case of AIDS, for example, experts report that between 90% and 100% of applications are off-label.<sup>15</sup> According to a representative of the American Medical Association, "[i]n some cases, if you didn't use the drug in the off-label way, you'd be guilty of malpractice."<sup>16</sup> As one author bluntly stated,

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<sup>11</sup> GAO Report, supra note 2, at 40; id. at 3, 11 ("A third of all drug administrations to cancer patients were off-label, and more than half of the patients received at least one off-label drug. . . . [I]t is even possible that for a specific form of cancer, a drug given off-label may have been proven to be more beneficial than any drug labeled for that cancer.").

<sup>12</sup> Id. at 21-22.

<sup>13</sup> See FDA, Single Issue Focus Meeting, Section 401 of the FDA Modernization Act: Dissemination of Information on Unapproved New Uses for Marketed Drugs, Biologics, and Devices, at 14 (July 8, 1998) <<http://www.fda.gov/ohrms/dockets/dockets/98n0222/tr00001.txt>>.

<sup>14</sup> GAO Report, supra note 2, at 11.

<sup>15</sup> See Kenneth P. Berkowitz et al., Congress Tries To Bridge the "Label Gap," but Nobody Is Cheering, Med. Mktg. & Media, Jan. 1998, at 40, 42.

<sup>16</sup> Beck & Azari, supra note 4, at 80 (citing Fran Kritz, FDA Seeks To Add Drugs' New Uses to Labels, Wash. Post, Mar. 29, 1994, at Z11 (quoting American Medical Association vice-president)).



"[o]bviously, many more people would die, and the clamor about FDA-induced 'drug lag' would be more intense, if off-label prescriptions were suppressed."<sup>17</sup>

Through off-label use, physicians discover new, more effective means of treating their patients. The FDA Drug Bulletin reported that when physicians resort to off-label use of drug products, they often discover "[v]alid new uses for drugs already on the market . . . through [their] serendipitous observations and therapeutic innovations."<sup>18</sup> The great majority of breakthroughs in treating depression and schizophrenia come through unapproved uses, as have nearly all curative anti-cancer therapies.<sup>19</sup>

Off-label uses are especially common in pediatric populations. See Washington Legal Found., 13 F. Supp. 2d at 56 (observing that off-label uses are important to pediatrics). In fact, FDA recognizes that many off-label uses are the norm in pediatrics, often because testing in children can be prohibitively expensive and because involving children in clinical trials raises special concerns not present with respect to adult testing.<sup>20</sup> As a result of the costs, risks, and unique difficulties involved in bringing pediatric uses on-label for a drug only approved for uses

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<sup>17</sup> Krauss, supra note 3, at 473.

<sup>18</sup> Unlabeled Indications, supra note 9, at 5.

<sup>19</sup> See Robert M. Goldberg, Breaking up the FDA's Medical Information Monopoly, 1995 Regulation: Cato Rev. of Bus. & Gov't, No. 2, at 48.

<sup>20</sup> See WLF Mem., supra note 10, at 7 (citing Temple Tr. 54; David Kessler, Speech of FDA Commissioner to the American Academy of Pediatrics (Oct. 14, 1992); Hubbard Tr. 164, 77-78); infra pp. A-23 to A-25 (discussing unique problems associated with pediatric testing, including separation from parents, discomfort, fear, and difficulty in obtaining blood samples).

in adult populations, most drugs carry a disclaimer stating that safety and effectiveness have not been tested in children.<sup>21</sup>

FDA has attempted to justify the Pediatric Rule by saying that "the absence of pediatric labeling information poses significant risks for children." 63 Fed. Reg. at 66,632. Yet off-label pediatric uses, like other off-label uses, are not unduly risky. "Off-label" merely means that the label is "silent" as to that particular use. Such uses pose no great safety hazard because "FDA premarket review of drugs involves [such] extensive scrutiny [that] the agency ordinarily has reasonable assurances that marketed products are safe, both for their labeled uses and for general use."<sup>22</sup> Neither does any correlation necessarily exist between the off-label versus on-label status of a use and the benefits of that use.<sup>23</sup> As the GAO Report stated, "[t]he category 'off-label use' runs from clearly experimental use to standard therapy and even to state-of-the-art treatment."<sup>24</sup>

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<sup>21</sup> See Lawrence Bachorik, Why FDA Is Encouraging Drug Testing in Children, FDA Consumer, July-Aug. 1991, at 15 (interview with Paula Botstein, M.D., Deputy Director of FDA's Office of Drug Evaluation I) (stating that because population of children is small, financial return of studying drugs in children is small); 21 C.F.R. § 201.57(f)(9)(v) (1999) (requiring explicit disclaimer on label of drugs not approved for pediatric populations); Reauthorization of the Prescription Drug User Fee Act and FDA Reform: Hearings Before the Subcomm. on Health and Environment of the House Commerce Comm., 105th Cong. (Apr. 23, 1997) (statement of Sanford N. Cohen, American Academy of Pediatrics) ("Eighty percent or more of drugs approved since 1962 have been approved and labeled for use in adults with a disclaimer that they are not approved for use by children.") [hereinafter "Cohen Testimony"].

<sup>22</sup> Beck & Azari, supra note 4, at 82.

<sup>23</sup> See id. at 72 ("All medical treatments, including off-label treatments, have medical risks. . . . The mere fact of off-label use . . . is a matter solely of FDA regulatory status and cannot logically be considered a medical risk of a drug or medical device. Nor is off-label use inherently experimental or investigational." (citation omitted)).

<sup>24</sup> GAO Report, supra note 2, at 11.

If anything, off-label pediatric uses arguably represent a less risky alternative for children than does FDA's Pediatric Rule. Drugs used off-label in pediatric populations have already been established to be safe and effective for use in adult populations. See 21 U.S.C. § 355(d) (1994 & Supp. III 1997) (requiring that drug be safe and effective "for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof"). Moreover, doctors prescribing drugs off-label to children will do so on a one-on-one basis, in the context of a doctor-patient relationship. The Pediatric Rule, by contrast, pressures manufacturers in the context of clinical studies – which involve groups of patients rather than the highly individualized setting of a doctor-patient relationship – to administer those same drugs to children before they are approved for use on adults. See 21 C.F.R. § 314.55(a) (1999) (requiring new drug sponsors to submit "data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective"). Common sense dictates that the individualized administration to children in the context of a doctor-patient relationship of drugs already established to be safe and effective for adults represents an alternative that is at least as safe – if not far safer – than forcing manufacturers to test unapproved drugs on groups of children in the context of clinical studies.

Congress has recognized the well-established benefits of off-label uses. Specifically, it has expressly forbidden FDA from interfering with those uses, thus enabling physicians to take advantage of the latest advances in medical technology in treating their patients:

[I]t has been the long held view of Congress that the FDA should not regulate the practice of medicine. In general, the FDA has no authority to regulate how physicians prescribe approved drugs in the context of their medical practice. Physicians prescribing off-label uses of approved drugs is not within the jurisdiction of the FDA.

H.R. Rep. No. 105-310, at 60 (1997); see also 21 U.S.C. § 396 (Supp. III 1997) (exempting practice of medicine from Food, Drug, and Cosmetic Act); H.R. Conf. Rep. No. 105-399, at 97, reprinted in 1997 U.S.C.C.A.N. 2880, 2887 (warning that "the FDA should not interfere in the practice of medicine" and that physician-prescribed off-label use of medical devices "is not the province of the FDA"). Likewise, Congress allows reimbursement under the Medicare and Medicaid programs for off-label prescriptions. See 42 U.S.C. §§ 1396b, 1396r-8 (1994 & Supp. III 1997).<sup>25</sup>

At the same time, Congress recognizes that there is some benefit in encouraging manufacturers to seek FDA approval for off-label uses to keep the drug label up to date – so long as the FDA approval process does not obstruct the availability of effective treatments to prescribing physicians and their patients:

Although the use of an approved product for an unapproved use does not violate the law, it is important to encourage the addition of new uses to the FDA-approved product labeling in order to keep that labeling current with medical practice.

H.R. Rep. No. 105-310, at 63; see also S. Rep. No. 105-43, at 42 (1997). To encourage manufacturers voluntarily to seek approval for off-label indications – while at the same time ensuring that FDA did not exceed its statutory authority – Congress included various incentives in FDAMA. The Pediatric Rule undercuts that regime, substituting compulsion for cooperation.

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<sup>25</sup> See also FDA, Public Hearing on Pharmaceutical Marketing and Information Exchange in Managed Care Environments (Oct. 19, 1995) <<http://www.fda.gov/cder/ddmac/MANAGEDCAREPANEL2.htm>> (statement of Pharmacist Calvin Knowlton on behalf of American Pharmaceutical Association) (stating that Medicare and Medicaid statutes "provide payment for off-label use of drugs if these uses are recognized as accepted medical practice under the authoritative compendia listed in the Federal Medicare and Medicaid statutes").

**B. The Pediatric Rule Is Inconsistent With FDAMA Provisions Designed To Encourage Manufacturers To Bring Off-Label Uses On-Label Voluntarily.**

**1. The Rule Is Inconsistent with the Pediatric Exclusivity Provision.**

In FDAMA, Congress enacted an elaborate voluntary incentive scheme whereby FDA may request pediatric studies for both new and marketed drugs if FDA determines that additional pediatric information concerning those drugs "may produce health benefits in the pediatric population." 21 U.S.C. § 355a (Supp. III 1997). If the manufacturer agrees to conduct, and FDA accepts, such studies, the manufacturer is entitled to an additional six months of marketing exclusivity under certain circumstances. *See id.* The statute also contains a sunset provision and a requirement that FDA report to Congress on this provision by January 1, 2001. *Id.* § 355a(j)-(k) (Supp. III 1997). Notably, FDA must discuss in its report (1) "the effectiveness of the program in improving information about important pediatric uses for approved drugs," (2) "the adequacy of the incentives provided under this section," and (3) "any suggestions for modification that the Secretary determines to be appropriate." *Id.* § 355a(k).

Although Congress only authorized FDA to request pediatric studies and to suggest appropriate modifications after the incentive program had been tested, FDA has promulgated regulations, far beyond its statutory mandate, which require manufacturers to conduct those same studies. Compare 21 U.S.C. § 355a(a), (c) (Supp. III 1997) (authorizing FDA to "make[] a written request for pediatric studies" from manufacturers of new and marketed drugs) and S. Rep. No. 105-43, at 3 ("The legislation gives the Secretary authority to request pediatric clinical trials for new drug applications and provides 6 extra months of market exclusivity to drugs when the manufacturer voluntarily meet[s] certain conditions under the program.") with 21 C.F.R.

§ 201.23(a) (1999) (providing that manufacturer of marketed drug "may be required to submit an application containing data adequate to assess" safety and effectiveness of drug, including dosage and administration in some or all pediatric subpopulations and "may also be required to develop a pediatric formulation") and id. § 314.55 (1999) (requiring new drug manufacturers to conduct pediatric studies and develop pediatric formulations). It makes little sense for Congress to have enacted legislation that "gives the Secretary authority to request pediatric clinical trials" and provides substantial incentives to induce manufacturers to agree to conduct such studies - if all along the Secretary had authority to require those same studies, thus largely negating the elaborate congressional scheme.

It is particularly inappropriate for FDA to contradict these explicit congressional provisions in light of their obviously experimental nature. Not only did Congress include a sunset provision in the legislation, but it also expressly required FDA to report to Congress concerning the effectiveness of the legislation, including any suggestions that FDA could offer to improve the scheme. 21 U.S.C. § 355a(j)-(k). Rather than heed these explicit directives by giving Congress's scheme the benefit of the statutorily mandated trial run, however, FDA instead proclaimed that it "does not believe . . . that incentives alone will result in pediatric studies of some of the drugs and biologics where the need is greatest." 63 Fed. Reg. at 66,639. Rather, FDA declared its "belie[f] that a mixture of incentives and requirements is most likely to result in real improvements in pediatric labeling." Id. FDA provided no evidence to support this "belief." Instead, it pointed out that, under FDAMA, incentives are not available for many products. See id.

Contrary to FDA's pessimistic view of the efficacy of the pediatric exclusivity provisions in FDAMA, many manufacturers have already decided to take advantage of these provisions. To

illustrate, as of October 1, 1999, manufacturers had already filed 159 proposed pediatric study requests with FDA.<sup>26</sup> Of those 159 requests, FDA had acted on 157.<sup>27</sup> Nine active moieties, including six approved active moieties, have already received extended exclusivity as a result of pediatric testing.<sup>28</sup> Most of the drugs that are currently benefiting from the extended pediatric exclusivity provisions are approved, marketed drugs rather than new drugs. FDA has stated that it would require pediatric testing for approved drugs "only in compelling circumstances," which it estimates will exist for "approximately two marketed drugs per year." 63 Fed. Reg. at 66,654.

In light of this experience, FDA should reconsider its assertion that the FDAMA procedures will be insufficient to bring about pediatric testing and revoke the Pediatric Rule. 63 Fed. Reg. at 66,639; see Home Box Office, Inc. v. FCC, 567 F.2d 9, 36 (D.C. Cir. 1977) ("[A] regulation perfectly reasonable and appropriate in the face of a given problem may be highly capricious if that problem does not exist." (internal quotations omitted)); see also Texas v. EPA, 499 F.2d 289, 319 & n.49 (5th Cir. 1974) (observing that agency must rely upon data that is "the best that is feasibly available" and that agency has "duty to reconsider and revise its requirements as better data becomes available"). At a minimum, FDA should allow Congress's voluntary pediatric exclusivity scheme the congressionally mandated opportunity to prove its efficacy.

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<sup>26</sup> See FDA, Center for Drug Evaluation and Research, Pediatric Exclusivity Statistics (last modified Oct. 1, 1999) <<http://www.fda.gov/cder/pediatric/wrstats.htm>>.

<sup>27</sup> See id.

<sup>28</sup> See FDA, Center for Drug Evaluation and Research, Approved Active Moieties to Which FDA Has Granted Exclusivity for Pediatric Studies Under Section 505A of the Federal Food, Drug, and Cosmetic Act (last modified Oct. 29, 1999) <<http://www.fda.gov/cder/pediatric/exgrant.htm>> (listing grants of pediatric extended exclusivity for six approved active moieties, including grants for ibuprofen to two different sponsors).



## 2. The Rule Conflicts with the Supplemental Application Provision.

A second provision demonstrating that Congress intended to encourage - not force manufacturers to seek approval for off-label uses concerns supplemental applications for new uses of approved drugs. See 21 U.S.C. § 371 note (Supp. III 1997). The provision accomplishes this by, inter alia, establishing mechanisms by which FDA can "encourag[e] the prompt review of supplemental applications" and "work[] with sponsors to facilitate the submission of data to support supplemental applications." Id. According to an accompanying House Report, the purpose of the legislation is to "encourage the regulated industry to submit supplemental applications whenever feasible" for new uses of approved products and to do so by "reducing the overall burden of submitting supplemental applications and obtaining their approval." H.R. Rep. No. 105-310, at 64.

Congress had a compelling practical reason for structuring FDAMA to allow off-label uses to continue rather than to forcing those uses on-label immediately - medical discoveries happen faster than FDA can possibly track:

New uses for drugs are often discovered after FDA approves the package inserts that explain a drug's approved uses. Congress would have created havoc in the practice of medicine had it required physicians to follow the expensive and time-consuming procedure of obtaining FDA approval before putting drugs to new uses.

United States v. Algon Chem. Inc., 879 F.2d 1154, 1163 (3d Cir. 1989).<sup>29</sup>

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<sup>29</sup> See William L. Christopher, Off-Label Drug Prescription: Filling the Regulatory Vacuum, 48 Food & Drug L.J. 247, 261 (1993) (stating that FDA "could not review drugs at a pace equal to that at which physicians discover beneficial off-label uses").

Many states have statutes endorsing the use of off-label drugs. For example, N.J. Stat. Ann. § 26.1A-36.9(g) (1996) contains the following statement:

(Continued...)



Despite Congress's clear intent to allow off-label uses to continue and merely encourage – rather than require – that those uses be brought on-label, the Pediatric Rule requires manufacturers of marketed drugs to seek approval for off-label pediatric uses. Moreover, although the goal of the supplemental application provision is to “reduc[e] the overall burden of submitting supplemental applications and obtaining their approval,” the Pediatric Rule increases that burden by requiring manufacturers not only to conduct clinical studies to support pediatric uses, but also to develop entirely new formulations appropriate for various pediatric subpopulations. See 21 C.F.R. § 201.23(a) (requiring manufacturer of marketed drug “to

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(... Continued)

“Off-label” use of FDA-approved drugs provides efficacious drugs at a lower cost. To require that all appropriate uses of a drug undergo approval by the FDA may substantially increase the cost of drugs and delay or even deny patients’ ability to obtain medically effective treatment. FDA approval for each use would require substantial expenditure and time to undergo the clinical trials necessary to obtain FDA approval.

This widespread consensus that a drug regulatory scheme permitting off-label uses is superior to one that does not stems from the notion that market forces, rather than the government, can most efficiently determine the uses and the patient populations for which drugs should be marketed. As one commentator has observed, “the clinical judgment of the marketplace is more effective and quicker than the FDA regulatory scheme in making the comparisons required to determine what drugs work and for whom.” Goldberg, supra note 19, at 42; see Doug Bandow, The FDA Can Be Dangerous to Your Health, Cato: This Just In (Jan. 29, 1997) <<http://www.cato.org/dailys/1-29-97.html>> (“[E]ffectiveness is best tested in the marketplace.”). Indeed, economic studies, along with many years of FDA and drug manufacturer experience, demonstrate that market forces have provided manufacturers with the incentive to design and produce safe drugs, particularly if tort remedies are available as a disincentive. See Krauss, supra note 3, at 459 (citing A. Mitchell Polinsky, An Introduction to Law and Economics (1983)). Thus, private drug companies as market actors, and physicians and patients making individualized health decisions – rather than the government – are better able to respond to the medical, pharmaceutical, toxicologic, ethical, and resource considerations involved in deciding whether to market a drug to pediatric populations.

develop a pediatric formulation" in certain instances). In short, the Pediatric Rule contradicts the supplemental application provision.

**C. Judicial Precedent Establishes That FDA Cannot Superimpose Its Own Conflicting Scheme Of Mandatory Pediatric Regulations On Congress's Voluntary Scheme.**

Judicial precedent confirms that FDA may not superimpose its own mandatory system of regulations on Congress's dramatically different, voluntary scheme, addressing the identical area of law. As the Supreme Court has long recognized, it is "an elemental canon of statutory construction that where a statute expressly provides a particular remedy or remedies, a court must be chary of reading others into it. When a statute limits a thing to be done in a particular mode, it includes the negative of any other mode." Transamerica Mortgage Advisors, Inc. v. Lewis, 444 U.S. 11, 20 (1979) (internal quotations omitted). Applying this well-established canon in Transamerica Mortgage Advisors, the Supreme Court refused to recognize private causes of action for damages for violations of a statute that "nowhere expressly provides for a private cause of action." Id. at 14, 19-20. After observing that "Congress expressly provided both judicial and administrative means for enforcing compliance," the Court concluded that "it is highly improbable that Congress absentmindedly forgot to mention an intended private action." Id. (internal quotations omitted).

The D.C. Circuit reached a similar conclusion in considering the propriety of the National Mediation Board's assertion of authority to investigate representation disputes among a carrier's employees. See Railway Labor Executives' Ass'n v. National Mediation Bd., 29 F.3d 655, 658-59 (en banc), amended by 38 F.3d 1224 (D.C. Cir. 1994). In light of a statute that provided for such investigations to be initiated "upon request of either party to the dispute," the court held that

the Board had exceeded its jurisdiction by initiating dispute investigations sua sponte given that "Congress effectively has provided a 'who, what, when, and how' laundry list governing the [agency's] authority." *Id.* at 665, 667. The court further observed that "[t]he duty to act under certain carefully defined circumstances simply does not subsume the discretion to act under other, wholly different, circumstances, unless the statute bears such a reading." *Id.* at 671.

Applying this judicial reasoning to the context of the Pediatric Rule, where Congress has enacted a detailed statutory scheme granting FDA limited authority to request that manufacturers voluntarily conduct pediatric studies of certain drugs, FDA cannot assert the authority to require manufacturers to conduct those studies. Moreover, where, as here, Congress expressly gave FDA authority to request pediatric studies, "it is highly improbable that Congress absentmindedly forgot to mention" that it also intended to grant FDA authority to require those same studies.

**D. The Serious Ethical Problems That Arise From The Mandatory Nature Of The Pediatric Rule Confirm The Superiority Of Congress's Incentive-Based Solution.**

The disturbing ethical problems that arise from the Pediatric Rule's requirement of mandatory testing of drugs in children – problems that are minimized by use of a voluntary pediatric testing scheme – further confirm the superiority of Congress's incentive-based scheme over the mandatory Pediatric Rule. First, the Pediatric Rule pressures manufacturers to conduct pediatric testing before a drug has been established as safe for adults. Second, by presuming that all drugs should be tested in children, the Pediatric Rule exacerbates the special risks involved in pediatric testing.

**1. The Pediatric Rule Increases the Risk of Pediatric Testing Before a Drug Is Shown To Be Safe for Adults.**

The domestic and international medical communities, as well as FDA, agree that pediatric testing generally should be deferred until Phase 2 or Phase 3 of the clinical research process. The American Academy of Pediatrics, for example, pointed out "without hesitation" in its response to FDA's proposed rulemaking that researchers should complete Phase 1 and part of Phase 2 before beginning pediatric testing.<sup>30</sup> The international community likewise acknowledges that "[w]hen pediatric patients are included in clinical trials, safety data from previous adult human exposure would usually represent the most relevant safety data and should generally be available before pediatric clinical trials."<sup>31</sup> Acting together with parallel regulatory bodies in Europe and Japan, FDA co-sponsored and endorsed the international agreement that made this assertion.<sup>32</sup> FDA

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<sup>30</sup> Letter from American Academy of Pediatrics to FDA Dockets Management Branch re Docket No. 97N-0165, Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, at 1, 5 (Nov. 13, 1997) [hereinafter "AAP Comments"]; see Committee on Drugs for the American Academy of Pediatrics, Guidelines for the Ethical Conduct of Studies To Evaluate Drugs in Pediatric Populations, 95 Pediatrics 286, 287 (1995) (stating that "studies in children should be preceded by initial clinical trials in adults to provide preliminary pharmacokinetic, safety, and efficacy data") [hereinafter "Ethical Guidelines"]; see also FDA, Public Meeting on FDA's Proposed Regulation to Increase Pediatric Use Information for Drugs and Biologics (Oct. 27, 1997) <<http://www.fda.gov/cder/meeting/transcript/1027pedi.htm>> (remarks of Dr. McCarthy, senior research fellow at the Kennedy Center for Bioethics, Georgetown University) ("I would make sure that the studies are at least through Phase II in adults before you move to children, and I would like to see it in two or three phases – older children, then younger children, and finally infants.") [hereinafter "Public Meeting"]; *id.* (remarks of Dr. Spielberg) ("[P]ediatric studies in general should not be initiated with a new chemical entity prior to the establishment of the adult dose, serum concentration profile, and a clear 'go' decision for the drug development process.").

<sup>31</sup> International Conference on Harmonisation, Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, 62 Fed. Reg. 62,922, 62,925 (1997).

<sup>32</sup> *Id.* at 62,922 (stating that FDA "is committed to seeking . . . harmonized technical procedures"). Similarly, the European Committee for Proprietary Medicinal Products ("CPMP") (Continued...)

also expressed its commitment to deferring pediatric testing in a 1977 report entitled General Considerations for the Clinical Evaluation of Drugs in Infants and Children when it stated that, "[b]ecause of ethical considerations, reasonable evidence of efficacy generally should be known before infants and children are exposed to the agent."<sup>33</sup>

Congress's voluntary incentive scheme minimizes the risks arising from concurrent pediatric testing. Because adult drug approval does not hinge upon successful completion of pediatric testing, there is no pressure on manufacturers to rush pediatric testing. Rather, the manufacturers, after consulting with appropriate medical professionals, may determine the appropriate timing and circumstances under which to initiate pediatric testing, first ensuring that the product is safe for adults.

By contrast, the Pediatric Rule's mandatory approach exerts enormous pressure on manufacturers to conduct concurrent pediatric testing, given that their drug products cannot be approved and marketed until safety and efficacy testing is complete. See 21 C.F.R. § 314.55(a).

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(... Continued)

determined that, "In general, safety studies should be conducted first in animals as a part of the routine pre-clinical development, then in adults, and subsequently in younger patients." European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, Note for Guidance on Clinical Investigation of Medicinal Products in Children, at 2 (Mar. 17, 1997). The age categories for pediatric testing also conflict with those set forth in the CPMP. See id. at 4-5. Such inconsistencies in timing requirements and age categories could force sponsors engaged in the international pharmaceutical market to conduct duplicative studies, thereby exposing more children than necessary to the risk of drug testing, resulting in what one drug manufacturer has called a "tremendously wasteful" allocation of resources. Letter from Glaxo Wellcome Research and Development to FDA Dockets Management Branch re Docket No. 97N-0165, Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, at 15 (Nov. 12, 1997) [hereinafter "Glaxo Wellcome Comments"].

<sup>33</sup> FDA, General Considerations for the Clinical Evaluation of Drugs in Infants and Children, at 5 (1977) [hereinafter "General Considerations in Infants and Children"].

Manufacturers naturally will try to place valuable new treatments into the hands of adults who need them as expeditiously as possible. The Pediatric Rule, however, hinders manufacturers' efforts to do so by requiring that, before adults may have access to the new drug, it must first be approved as safe and effective for use in children. Thus, FDA has limited manufacturers to three undesirable choices:

- (1) test the drug on children sooner rather than later to minimize the delay in providing it to ailing adults, thus triggering the ethical concerns discussed above by prematurely testing a product on children;
- (2) test the drug on adults first to ensure that it is safe and effective before testing it on children, thereby causing undesired, and potentially life-threatening, delays in making the treatment accessible to adults; or
- (3) redirect research and development efforts away from diseases occurring in both adults and children and toward diseases occurring exclusively in adults to avoid this conundrum altogether, ultimately harming children by limiting the quantity and quality of available pediatric treatments, both off-label and on-label.

In light of these alternatives, FDA's claim that "[n]othing in the rule requires concurrent testing in adults and pediatric patients, nor testing in infants and neonates before testing in older children," 63 Fed. Reg. at 66,642, rings hollow.

Nor does FDA's reliance upon the Pediatric Rule's deferral provisions solve this dilemma. See id. ("[I]ndustry comments appear to have misunderstood the explicit deferral provisions of the rule and perceived them as rare exceptions to a usual requirement that adults and children be studied at the same time."); id. at 66,640 (arguing that "the rule will not require studies in settings where ethical or medical concerns militate against studies" and that the Rule's deferral provisions are "specifically designed to ensure that no pediatric study begins until there are sufficient safety and effectiveness data to conclude that the study is ethically and medically appropriate"). Those provisions are merely exceptions to the general rule that all pediatric

testing must be completed before a drug can be approved and marketed. See 21 C.F.R. § 314.55(a).

Moreover, FDA has indicated that deferral should rarely be granted. FDA, for example, refused one pharmaceutical company's request to recognize circumstances in which FDA would automatically grant deferral. Instead, FDA adopted rules that give FDA complete discretion to determine whether deferral is appropriate. See id. § 314.55(b) (1999); 63 Fed. Reg. at 66,643 ("The need for deferral must be considered case-by-case."). FDA has further warned that deferral is not "necessarily warranted where analytic tools and clinical methodologies cannot be easily adapted to pediatric patients," nor are "[d]ifficulties in developing an adequate pediatric formulation" likely grounds for obtaining a deferral. Id. at 66,644.

Even in the rare instances where deferral may be granted, the Pediatric Rule places a high premium on testing new drugs on children as early as possible. Applications for deferral must not only "provide a certification from the applicant of the grounds for delaying pediatric studies" and "a description of the planned or ongoing studies," but they must also include "evidence that the studies are being or will be conducted with due diligence and at the earliest possible time." 21 C.F.R. § 314.55(b).<sup>34</sup>

In sum, FDA has done little to address legitimate concerns that the Pediatric Rule essentially mandates concurrent testing. Rather, it has summarily dismissed these concerns, leaving ethical issues unanswered and raising additional concerns about how it will apply this

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<sup>34</sup> In light of this substantial premium placed on early drug testing on children, FDA's other proffered justification of the safety of the Rule – i.e., that "no pediatric study may go forward without the approval of an [Institutional Review Board], which is responsible for ensuring that the study is ethical and adequately protects the safety of the subjects" – provides little comfort. 63 Fed. Reg. at 66,640.

new mandate. This response is insufficient as a matter of law. See, e.g., Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983) (holding that "agency must examine the relevant data and articulate a satisfactory explanation for its action").

It is particularly troublesome for FDA to subject children to the risk of concurrent testing where the vast majority of that testing will ultimately prove unnecessary. Only a tiny fraction of all new drugs actually obtain FDA approval to be marketed, and thus are ever used by children. Of the drugs that begin human clinical testing, "[o]nly 23% . . . eventually receive marketing approval." Drugs and Biologics – A Consumer's Perspective: Hearings Before the Subcomm. on Oversight and Investigations of the House Commerce Comm., 104th Cong. (May 25, 1995) (written testimony of Kenneth Kaitin) [hereinafter "Kaitin Testimony"].<sup>35</sup> As one commenter observed, "up to 50% of drugs are abandoned before phase 3." See 63 Fed. Reg. at 66,643. Even for the drugs that successfully reach Phase III, FDA itself has estimated that "only about 65% of all [new molecular entities] that enter phase III trials are eventually approved." Pediatric Patients: Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products: Proposed Rule, 62 Fed. Reg. 43,900, 43,911 (1997); accord

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<sup>35</sup> See Krauss, supra note 3, at 462 ("Only one out of 5,000 new drugs now complete [the drug approval] process successfully.").

<sup>36</sup> Accord David A. Kessler, The Regulation of Investigational Drugs, 320 New Eng. J. Med. 281, 282 (1989) ("[T]he vast majority of preliminary drug studies do not lead to marketing applications.").

<sup>37</sup> FDA's position in the Pediatric Rule is that pediatric testing for products meant to cure serious diseases that are less than life-threatening should begin when data is available "from the initial well-controlled studies in adults" – i.e., at the end of Phase II. 63 Fed. Reg. at 66,643.



Kaitin Testimony, supra p. A-21 (stating that only 64% of the drugs that begin Phase III testing eventually receive market approval).

These "drug dropout" rates establish that the Pediatric Rule will subject children to risky testing of products that will never even be marketed in the U.S.<sup>38</sup> Indeed, by FDA's own calculations, fully thirty percent of the children who would be exposed to drug testing under the Pediatric Rule would be needlessly put at risk. 62 Fed. Reg. at 43,911 (increasing estimate of pediatric studies required by 30% to account for testing of "drugs that ultimately fail to gain regulatory approval"); accord 63 Fed. Reg. at 66,662-63 (affirming prior calculations). FDA's estimate conservatively assumes that manufacturers would conduct no pediatric testing until Phase III or later. See 62 Fed. Reg. at 43,911. If some pediatric testing occurred before Phase III, the number of children needlessly put at risk would be even higher than FDA's 30% estimate.

To expose children to huge risks unnecessarily, even before minimal safety and efficacy of drugs for adults has been established, violates the whole purpose of the Pediatric Rule, which is purportedly to make treatments safer for children. In addition, this potential exposure highlights the superiority of Congress's voluntary approach to pediatric testing. That approach

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<sup>38</sup> See Public Meeting, supra note 30 (statement of Dr. Walson, Division Head, Clinical Pharmacology/Toxicology, at Children's Hospital in Columbus, Ohio) (referring to "negative guinea pig image of [pediatric] research").

<sup>39</sup> FDA's assumption that only 30% of pediatric testing will be unnecessary is inconsistent with its position that "[p]ediatric studies of drugs and biologics for life-threatening diseases may in some cases be appropriately begun as early as the initial safety data in adults becomes available." 63 Fed. Reg. at 66,643.

allows for maximum flexibility in ensuring that such testing is both necessary and safe before its initiation.<sup>40</sup>

## **2. The Pediatric Rule Exacerbates the Special Risks and Difficulties Involved in Pediatric Testing.**

The Pediatric Rule's requirement that new drugs be universally tested on children unless FDA affirmatively waives the requirement also unnecessarily aggravates the special problems involved in conducting pediatric testing. As Dr. Clemente, founder and Chairman of the Board of Ascent Pediatrics, explained during hearings on the Pediatric Rule, "[t]esting in children is different and it is also very demanding and expensive for a number of reasons, such as the limitation of qualified study sites, the identification of appropriate patients, [and] parents['] reluctan[ce] to enroll their children in a clinical study."<sup>41</sup> Additionally, "[t]here are practical considerations, such as obtaining blood and urine samples, [and] difficulty in obtaining outcome data as children may not be able to describe symptoms or side effects."<sup>42</sup> These practical considerations can make it difficult to develop appropriate methodologies to assess a drug's safety and effectiveness in children as well as to implement adequate behavioral safeguards for studies. Other problems include obtaining informed consent,<sup>43</sup> the limited number of

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<sup>40</sup> This potential for harm undercuts FDA's former position that "[a] prime requirement [of clinical investigation] is that the subjects (patients) are exposed to the least possible risk consistent with anticipated benefit." FDA, General Considerations for the Clinical Evaluation of Drugs (1977), at ii; accord id. at 1.

<sup>41</sup> Public Meeting, supra note 30 (remarks of Dr. Clemente).

<sup>42</sup> Id.

<sup>43</sup> See Ethical Guidelines, supra note 30, at 292 (observing that "obtaining truly informed consent may be difficult [in children with chronically progressive or potentially fatal diseases] because of the child's debilitated condition or the mental and emotional state of the parents").

investigators who have expertise to conduct trials in young children, and determining appropriate timing of clinical trials in light of the child's maturation.<sup>44</sup> Additionally, special risk factors apply to children, including "discomfort, inconvenience, pain, fright, separation from parents or familiar surroundings [and] effects on growth or development of organs."<sup>45</sup>

Yet another barrier to conducting clinical trials in pediatric patients is the difficulty in enrolling sufficient numbers of children. Traditionally, studies of drug products in pediatric populations have involved sick children.<sup>46</sup> Without the prospect of a medical advance for their child, parents may have no incentive to enroll their children. In fact, at least one pediatric medical journal has declared that "[s]tudies that promise no demonstrable benefits to the child participating in the study or to children in general should not be conducted, irrespective of the minimal nature of the attendant risks."<sup>47</sup>

The scheme that Congress established in FDAMA minimizes such problems. Because pediatric testing is encouraged but not required, manufacturers can determine when, and whether, to conduct such testing. Manufacturers are therefore likely to defer testing until they are sure that the product will gain approval for use in adults and there is demonstrated pediatric interest, thus producing a potential "sick child" population for testing. This winnowing process will eliminate

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<sup>44</sup> Letter from Novartis Pharms. Corp. to FDA Dockets Management Branch re Docket No. 97N-0165, *Pediatric Patients: Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products: Proposed Rule*, at 3-4 (Nov. 13, 1997).

<sup>45</sup> Ethical Guidelines, *supra* note 30, at 288.

<sup>46</sup> See General Considerations in Infants and Children, *supra* note 33, at 5 ("Based on ethical considerations, sick children rather than well ones will be the principal source of the experimental population . . .").

<sup>47</sup> Ethical Guidelines, *supra* note 30, at 288.

a large number of products from consideration for testing on children. The Pediatric Rule, by contrast, exacerbates these problems by virtue of its universal mandatory approach to pediatric testing.

**E. Section 355a(i) Of FDAMA Does Not Allow FDA To Bootstrap Its Authority To Promulgate The Pediatric Rule.**

Contrary to FDA's claims, 21 U.S.C. § 355a(i) does not support its position that the Pediatric Rule is statutorily permissible and consistent with FDAMA. That provision awards extended market exclusivity to a drug for which a manufacturer has conducted pediatric studies that were "required pursuant to regulations promulgated by the Secretary" and that comply with the requirements of § 355a. See 21 U.S.C. § 355a. The provision, however, does not constitute an independent grant of statutory authority for FDA to require pediatric studies. See H.R. Rep. No. 105-310, at 54 (acknowledging that regulations requiring pediatric studies must be "promulgated under other authorities of law"); National Pharm. Alliance v. Henney, 47 F. Supp. 2d 37, 41 (D.D.C. 1999) (acknowledging that, apart from congressionally enacted legislative incentives for pediatric testing, such testing "is not otherwise required of drug manufacturers"). Rather, it recognizes that there may be situations where FDA properly may require pediatric testing under preexisting statutory authorities, such as where a manufacturer declines to disclaim pediatric uses. As discussed in Appendices B and C below, FDA's rule goes far beyond its preexisting authorities. Section 355a(i), which deals with the consequences of properly required testing, cannot expand these authorities. See 21 U.S.C. § 355a(i) (Supp. III 1997).

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In sum, the Pediatric Rule is inconsistent with FDAMA's voluntary pediatric exclusivity and supplemental application provisions. It is, accordingly, an impermissible exercise of FDA's regulatory authority.

## **II. THE RULE CONFLICTS WITH CONGRESS'S GOAL OF STREAMLINING AND ACCELERATING THE DRUG APPROVAL PROCESS.**

Another of Congress's primary concerns in enacting FDAMA was the unreasonably long delay between a manufacturer's submission of a new drug application ("NDA") and FDA's approval of the application, as well as the substantial expense associated with that process. Since 1962, regulation by FDA has more than doubled the development costs for drugs and has significantly delayed the introduction of new drugs to the United States market.<sup>48</sup> A study that was reported in 1992 estimated that "the cost of bringing a new drug to market" had increased 230% over a fifteen-year time period.<sup>49</sup> From 1963 to 1975, the average cost of developing a new drug was \$125 million. From 1981 to 1990, the cost averaged \$394 million.<sup>50</sup> Average drug review time has almost doubled from two years in 1962 to more than three years in 1989, and the time required to gather data has more than doubled from three years to between six and seven years.<sup>51</sup>

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<sup>48</sup> See Sam Kazman, Deadly Overcaution: FDA's Drug Approval Process, J. Reg. & Soc. Costs, Sept. 1990, at 35-36.

<sup>49</sup> See Michael R. Ward, Drug Approval Overregulation, 1992 Regulation: Cato Rev. of Bus. & Gov't, No. 4, at 49; see also The Cato Institute, Handbook for Congress (105th Congress), at 342 (1998) (stating that cost of drug development has increased by over 400% in less than two decades).

<sup>50</sup> See Goldberg, supra note 19, at 45.

<sup>51</sup> See Ward, supra note 49, at 49.

While cost and delay have dramatically increased, the number of unsafe drugs has not declined correspondingly.<sup>52</sup> Moreover, the number of new drugs introduced in the U.S. has declined by fifty percent relative to other industrialized countries. Although the United States leads the world in researching, developing, and patenting valuable new drug treatments – from 1979 to 1989, the United States Patent and Trademark Office granted between 2,000 and 4,200 drug patents annually – increasingly onerous FDA regulation has significantly hampered the marketing of these products.<sup>53</sup> For example, for each year from 1964 to 1989, “pharmaceutical firms filed between 800 to 2,200 investigational new drugs with the FDA. . . . Of the 80 to 250 new drug applications firms file annually, the FDA approves only 20 to 60,” and “[m]any of those represent reformulations of existing products.”<sup>54</sup> Similarly, “[o]nly 27% of recently-approved new drugs in the U.S. were first marketed in this country; 54% were available one or more years in a foreign market prior to U.S. approval . . . . For biopharmaceutical products approved in the U.S., Europe, and Japan, 58% originated in the U.S., 47% began clinical testing in this country, but only 18% were first marketed here.” Kaitin Testimony, supra p. A-21. “In contrast, 57% were first marketed in Europe and 25% were first marketed in Japan.” Id.

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<sup>52</sup> See id.; see also Goldberg, supra note 19, at 43 (“[T]he FDA’s regulation of new drug approvals yields little in the way of additional safety. In fact, over the past 20 years the number of drugs that the FDA or manufacturers pulled from the market because of safety concerns has been insignificant both here and abroad. Worldwide only a handful of drugs have been discontinued for safety reasons, and little difference exists in the rate that unsafe drugs have been pulled from the market in the United States and the United Kingdom.”).

<sup>53</sup> See Ward, supra note 49, at 48.

<sup>54</sup> Id.

Unsurprisingly, FDA's onerous regulations have caused Britain to overtake the U.S. as the world leader in introducing new drugs to the market.<sup>55</sup>

Doctors are also highly dissatisfied with FDA's lengthy drug approval process. Recent polls commissioned by CEI revealed that "67% of the neurologists and neurosurgeons surveyed believe that the FDA takes too much time to approve new drugs and medical devices, and 58% agree that such delays cost lives."<sup>56</sup> Sixty-five percent of cardiologists and 77% of oncologists agree that FDA is too slow in approving new drugs and medical devices, and 57% of cardiologists and 47% of oncologists also agree that FDA's delay in approving drugs costs lives.<sup>57</sup> Eighty percent of neurologists and neurosurgeons "claim that the approval process, on at least one occasion, prevented them from treating their patients with the best possible care," while 71% of cardiologists and 63% of oncologists agree that "FDA's approval process has hurt [their] ability to treat [their] patients with the best possible care" on one or more occasions.<sup>58</sup>

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<sup>55</sup> See Kazman, *supra* note 48, at 40 ("From 1977 to 1987, 204 new drugs were introduced in the US; of these, 114 were available in Britain, with an average lead-time of more than five years per drug. On the other hand, of the 186 new drugs introduced into Britain during this period, only 41 were already available in the U.S. and then only by an average lead-time of two and a half years. As for exclusively available drugs, there were 70 in Britain but only 54 in the US."). Similarly, a Competitive Enterprise Institute publication reveals that it took FDA nearly two years to approve taxotere, a drug designed to treat advanced cases of breast cancer, while the Canadians had approved the drug in a year and the Europeans in 16 months. See Julie C. Defalco, Competitive Enterprise Institute, Treatment Delayed, Treatment Denied: Therapeutic Lag and FDA's Performance, at 2-3 (Feb. 1997).

<sup>56</sup> Competitive Enterprise Institute, A National Survey of Neurologists and Neurosurgeons Regarding the Food and Drug Administration, at 1 (Oct. 1998).

<sup>57</sup> *Id.* at 12 (citing surveys of oncologists and cardiologists commissioned by CEI in July 1996 and August 1995, respectively).

<sup>58</sup> *Id.* at 2, 14.

Congress recognized all of this. As a House Report discussing the proposed drug modernization legislation notes:

Currently, it takes nearly 15 years to develop a new drug – twice the time required in the 1960s. New scientific knowledge can produce effective new treatments for uncured diseases, but a drug development process slowed by outmoded regulation may mean that cures come too late for many patients.

Unfortunately, many patients do not have the time to wait the nearly 15 years it now takes to bring a new drug or biologic from the laboratory to the pharmacy shelf. . . .

Part of the reason for this growing development time is the increasing complexity of the diseases researchers are targeting. But an undeniable part of the delay in getting medicines to patients lies in the rules and regulations imposed by the FDA – requirements that add to development and approval time without enhancing the safety and effectiveness of new drugs and biologics.

H.R. Rep. No. 105-310, at 34-35. The Senate noted similar problems concerning the protracted, complex, and expensive nature of obtaining FDA approval to market a new drug:

Over the years, and particularly with the enactment of requirements that the FDA determine that drugs and devices are effective as well as safe, the FDA's requirements for clinical testing and its premarket reviews of new products have grown increasingly complex, time-consuming, and costly. From the 1960's to the 1990's, for example, the time required to complete clinical trials for new drugs has grown from 2.5 to nearly 6 years. Applications for the approval of new drugs typically run to hundreds of thousands of pages in length. According to a recently published study, from the beginning of the process to the end, it takes an average of 15 years and costs in the range of \$500 million dollars to bring a new drug to market.

S. Rep. No. 105-43, at 6.

To address this problem, Congress included a number of provisions in FDAMA intended to streamline and accelerate the drug approval process. For example, Congress enacted a fast-track approval process to "expedit[e] the approval of drugs and biological products that demonstrate the potential to address unmet medical needs for serious and life-threatening



conditions.” H.R. Rep. No. 105-310, at 54; 21 U.S.C. § 356 (1994 & Supp. III 1997). Likewise, Congress adopted provisions designed to “[s]treamlin[e] clinical research on drugs.” H.R. Rep. No. 105-310, at 69; 21 U.S.C. § 355(i) (1994 & Supp. III 1997). Further, Congress allowed FDA to approve an NDA based on only “one adequate and well-controlled clinical investigation and confirmatory evidence,” rather than the two investigations that FDA often had required. Id. § 355(d); see H.R. Rep. No. 105-310, at 67. Primary purposes underlying this latter provision were to:

reduce the number of patients required to undergo clinical trials and the possibility of receiving a placebo; reduce the cost of drug development, and thus, the ultimate cost of a new drug to the public; reduce the total time needed to obtain FDA approval of a new drug; increase the number of new drugs that can be investigated; and thus speed the development and availability of important new drugs to help improve the public health.

Id. at 68.

Far from making the drug approval process simpler, speedier, and less costly, however, the Pediatric Rule instead renders the process more expensive, protracted, and inefficient, as discussed in more detail below.

#### **A. The Pediatric Rule Further Delays Bringing Drugs To Market.**

The increased testing and formulation requirements of the Pediatric Rule will delay the drug approval process, directly contravening FDAMA’s goal of accelerating drug approvals. For example, one survey of drug manufacturers showed that it takes from five months to four years to develop a pediatric formulation.<sup>59</sup> Moreover, requiring additional clinical studies can only

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<sup>59</sup> See Letter from Pharmaceutical Research and Manufacturers of America to FDA Dockets Management Branch re Docket No. 97N-0165, Pediatric Patients: Proposed Rule Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products, at (Continued . . .)

hinder even further a drug approval process that is already subject to sharp congressional criticism for its protracted nature. See supra pp. A-26 to A-30.

Substantial social harm results from this unwarranted delay. Even “[b]y a conservative estimate, FDA delays in allowing U.S. marketing of drugs used safely and effectively elsewhere around the world have cost the lives of at least 200,000 Americans over the past 30 years.”<sup>90</sup> In the pediatric context, FDA’s extensive new testing and formulation requirements will further delay the access of new drugs to the market. This denial to the general population of these beneficial treatments will harm patients who are unable to obtain potentially lifesaving medication. Indeed, it will not only be adults who suffer because they are denied access to safe and effective treatments. Even the children that the Pediatric Rule purports to help will instead be harmed because they will no longer be able to obtain beneficial drugs on an off-label basis. As one commentator pointedly asked, “if a new drug will save lives after its approval, then how many lives were lost while it was being reviewed?”<sup>91</sup>

The difficulty of detecting the victims of FDA’s “drug lag” renders the harm even more insidious. When FDA approves a harmful drug too quickly, the political outcry of newspaper

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8 (Nov. 13, 1997) (citing informal survey of PhRMA member companies) [hereinafter “PhRMA Comments”].

<sup>90</sup> Bandow, supra note 29, at 1 (quoting Robert Goldberg of Brandeis University); see Gregory Conko, Slowing Down Drug Approval Could Prove Costly, USA Today, July 21, 1998, at 10A (“While the FDA approval process is intended to keep unsafe drugs off the market, its overcaution in reviewing new drug applications often keeps potentially life-saving therapies out of the hands of people who need them.”). For specific examples of lives lost due to overcaution, see Krauss, supra note 3, at 467-68.

<sup>91</sup> Kazman, supra note 48, at 47.

headlines, television coverage, and congressional hearings creates pressure on FDA. When FDA delays approval of a beneficial drug, however, the victims are "invisible."<sup>62</sup> The victims of drug lag and their families rarely know of the error and therefore cannot complain. The Pediatric Rule has only reinforced this harmful political incentive for FDA to be overcautious in approving drugs.<sup>63</sup> Thus, despite FDA's best intentions, the Rule, as a practical matter, may largely ignore the following admonition of even one of the Rule's most ardent supporters:

Remedies should avoid impeding availability of a necessary drug to non-pediatric populations [because t]he goal is to accomplish pediatric studies so the drug may be labeled for infants and children, not to deprive a non-pediatric population of an important drug.<sup>64</sup>

#### **B. The Pediatric Rule Increases The Costs Of Drug Approval.**

The Pediatric Rule also will lead to increased research and development costs, which will be borne by manufacturers and consumers alike.

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<sup>62</sup> See Walter E. Williams, The Argument for Free Markets: Morality vs. Efficiency, 15 Cato J., Nos. 2-3, at 183 (Fall/Winter 1995/96) ("In all interventionist policy there are those who are beneficiaries and those who are victims. In most cases, the beneficiaries are highly visible and the victims are invisible."); Kazman, supra note 48, at 41 ("As former FDA Commissioner Alexander Schmidt once stated, 'In all of FDA's history, I am unable to find a single instance where a Congressional committee investigated the failure of FDA to approve a new drug. But the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them. The message to FDA staff could not be clearer.'" (quoting H.G. Grabowski & J.M. Vernon, The Regulation of Pharmaceuticals, at 5 (1983))); Kazman, supra note 48, at 41-43 (contrasting reaction to erroneous approval with reaction to erroneous delay).

<sup>63</sup> See Ward, supra note 49, at 47 ("Drug approval stringency . . . exceed[s] what is socially optimal because the FDA is more adversely affected by approving harmful drugs than by denying approval of beneficial drugs."); Kazman, supra note 48, at 42 ("The political invisibility of drug lag's victims is the major reason for FDA's inherent overcaution in approving new drugs.").

<sup>64</sup> AAP Comments, supra note 30, at 6.

# **1. The Pediatric Rule Increases Manufacturer Costs.**

FDA has substantially underestimated the monetary cost of the studies that manufacturers must now conduct. In its Final Rule, FDA estimated the cost of the Rule to be \$46.7 million, a figure that was reached only after reducing the total cost of testing by 42% to account for costs that manufacturers purportedly would have incurred voluntarily. See 63 Fed. Reg. at 66,661. This estimate, however, does not accurately assess the number of children who must be studied for each drug. According to one prominent drug manufacturer, the Pediatric Rule will require testing of 34,000 patients per year, in contrast to FDA's extremely low estimate of 10,860.<sup>65</sup>

In addition to the increased manufacturer research costs, the Pediatric Rule will also lead to increased manufacturer development costs associated with the now-required development of pediatric formulations. Drug manufacturers who responded to FDA's proposal of the Pediatric Rule showed that FDA "grossly underestimated the number of drugs for which new formulations would be required."<sup>66</sup> Moreover, one survey showed that developing a pediatric formulation for a single drug product now costs between \$500,000 and \$3.5 million.<sup>67</sup> Taken together, the

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<sup>65</sup> Compare Letter from Wyeth-Ayerst Research to FDA Dockets Management Branch re Docket No. 97N-0165, Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Populations: Proposed Rule, at 6-7 (Nov. 13, 1997) with 63 Fed. Reg. at 66,663.

<sup>66</sup> See, e.g., Glaxo Wellcome Comments, supra note 32, at 14; see also id. at 2 ("The proposed new rule . . . will have a resource impact on the industry and FDA far greater than FDA has estimated . . .").

<sup>67</sup> See PhRMA Comments, supra note 59, at 8 (citing informal survey of member companies); id. at 25 ("Some companies have spent millions of dollars in efforts to develop a pediatric formulation and some have given up the pursuit after multiple efforts to develop a pediatric formulation have failed."); see also Public Meeting, supra note 30 (remarks of Dr. Clemente) ("[T]he formulation question is a very important one . . . a formulation for a child is truly a daunting avenue to approach.").

substantial number of products for which pediatric formulations likely will be necessary and the enormous development costs for each of those products equal a staggering increase in manufacturer expenditures to bring a new drug to market.

## **2. The Pediatric Rule Increases Consumer Costs.**

Drug companies will not be the only ones who suffer economic burdens as a result of the Pediatric Rule. Consumers also will pay an additional price because manufacturers will pass on at least some of their increased research costs to purchasers. By requiring the development of pediatric formulations, "the cost of some, if not most, adult formulations [will increase] due to the need to allow for the incremental and potentially high cost of development of such pediatric formulations."<sup>68</sup>

### **C. The Pediatric Rule Exacerbates The Inefficiencies Of The Drug Approval Process.**

Many drugs are of little or no use to pediatric populations. Moreover, creating pediatric formulations is difficult. Accordingly, establishing a presumption that manufacturers must test drugs on children and develop pediatric formulations will lead to an inefficient use of both FDA's and drug manufacturers' resources.

FDA, the American Academy of Pediatrics, and sponsors of drug development all agree that a large number of drugs, probably the majority, are of limited or no benefit to pediatric patients.<sup>69</sup> Yet despite these limited or nonexistent benefits for many drugs, the Pediatric Rule

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<sup>68</sup> Glaxo Wellcome Comments, supra note 32, at 11-12.

<sup>69</sup> See Cohen Testimony, supra note 21 (noting that "pediatric use represents a relatively small segment of the total market for a drug"); Pediatric Patients: Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products: Proposed Rule, 62 Fed. Reg. 43,900, 43,902 (1997) (observing that "[n]ot all [New Molecular

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presumptively requires pediatric testing and formulation development on all new drugs – and even some marketed drugs – and for “all relevant pediatric subpopulations,” including neonates, infants, children, and adolescents. 21 C.F.R. §§ 314.55(a), 201.23(a).

FDA’s reliance on the Rule’s waiver provisions in response to concerns that many drugs do not have pediatric uses is not reassuring. See 63 Fed. Reg. at 66,644-45. Although FDA asserts that the “rule is designed to require studies only in those settings in which there is a significant medical need or where usage among pediatric patients is likely to be substantial,” id. at 66,640, FDA continues to ignore that, by requiring all manufacturers to conduct testing absent a waiver, FDA creates a broad presumption that it will require such testing, not that it will limit such testing.<sup>70</sup> Even if FDA were to waive the requirement for most drugs, the mere process of requiring all manufacturers to compile data to support waiver requests and considering each request would largely be a wasted effort, resulting in a significant and unnecessary drain on both public and private resources.

Nor was FDA’s response to concerns that required testing in each pediatric age group would be excessive and unnecessary any more reassuring. Rather than addressing these concerns or providing further guidance in the preamble to the Pediatric Rule, FDA instead insisted that it

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Entities] have usefulness in pediatric patients”); Letter from Merck Research Laboratories to FDA Dockets Management Branch re Docket No. 97N-0165, Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, at 9 (Nov. 12, 1997) (“FDA and sponsors agree with the American Academy of Pediatrics that there are substantial numbers of drugs, probably the majority of those developed, which would be of limited or no benefit to pediatric patients.”); PhRMA Comments, supra note 59, at 20 (“Physicians caring for children use relatively few of the hundreds of drugs and biologics currently marketed.”).

<sup>70</sup> See, e.g., AAP Comments, supra note 30, at 4 (“Waivers should be granted RARELY”).

still believed that "studies in more than one age group may be necessary." *Id.*<sup>71</sup> FDA's Final Rule gives it absolute discretion to decide whether to waive testing requirements in particular pediatric age groups "if data from one age group can be extrapolated to another." 21 C.F.R. § 314.55(a). This response is insufficient as a matter of law. *See, e.g., State Farm*, 463 U.S. at 43 (holding that "agency must examine the relevant data and articulate a satisfactory explanation for its action").

The detrimental effects of this inefficient allocation of limited manufacturer drug development resources extend beyond mere economic inefficiencies. The regulations also will hamper valuable new drug innovation.<sup>72</sup> Requiring that drugs be tested concurrently in adults and children will further discourage sponsors from pursuing high risk projects.<sup>73</sup> The Pediatric

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<sup>71</sup> FDA's statement is even less assuring in light of the limited resources that it has to implement the rule. *See* Public Meeting, *supra* note 30 (statement of Dr. Temple, Executive Director of Medical Affairs at McNeil Consumer Products Company) ("Unless additional resources are provided, and unless additional help is available, the challenges to [FDA] to implement this proposed rule will be enormous. [FDA] will need much outside assistance.").

<sup>72</sup> *See* Goldberg, *supra* note 19, at 40 ("[T]he FDA's approval procedures have short-circuited the natural process of incorporating . . . information in the development of new products. The FDA in effect forces pharmaceutical companies to reinvent the wheel, thus driving up development costs."); *Handbook for Congress*, *supra* note 49, at 342 ("Just as control of information in despotic countries destroys creativity and innovation, the FDA's monopoly on the research, development, and use of new medical knowledge is choking off the next medical revolution."); Krauss, *supra* note 3, at 462 (observing that "substantial increases in the cost of developing a drug for the United States market," largely caused by FDA's "involvement in testing" . . . will "affect both the number of new drugs developed and the market price of developed drugs during their patent monopoly").

<sup>73</sup> *See* Glaxo Wellcome Comments, *supra* note 32, at 11-12 ("[S]uch a requirement during the investigational phases would necessitate diversion of resources from concurrent competing programs (e.g., development and testing of adult formulations). If resources are diverted from development of an adult formulation, the larger patient population would not be served and the sponsor would be less prepared to generate the pharmaceutical data necessary to achieve approval of the adult formulation.").

Rule will divert limited company resources from the research of new therapies to pediatric trials that explore limited, and possibly inappropriate, uses of existing products. By diverting resources, the Rule will hurt patients who await new life-saving discoveries.<sup>74</sup> It may even give companies an incentive to focus their research on diseases that almost exclusively affect adults.

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Although FDA claims the Rule is necessary to address the lack of adequate drugs approved for pediatric uses and to ensure that children will have safe and appropriate treatments available, the above discussion demonstrates that the Rule creates, rather than solves, problems. Moreover, the evidence that FDA cites in justifying the need for the Rule is scant and/or questionable.<sup>75</sup> FDA has failed to demonstrate that pediatric populations are being denied needed treatments, or that off-label uses of adult-use drugs are any less safe or effective than they would be if those uses were on-label. See Home Box Office, 567 F.2d at 36 (“[A] regulation perfectly reasonable and appropriate in the face of a given problem may be highly capricious if that problem does not exist.” (internal quotations omitted)); see also Northwest Airlines, Inc. v.

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<sup>74</sup> See Handbook for Congress, *supra* note 49, at 342 (observing that FDA’s drug approval process “is raising the cost of essential drugs and denying sick people access to lifesaving medicines”); Krauss, *supra* note 3, at 458 (observing that FDA’s “certification monopoly” over drugs “has arguably cost thousands of American lives”); *id.* at 471 (noting that “efforts to extend the FDA’s certification monopoly to off-label prescriptions have cost lives and money”).

<sup>75</sup> For example, FDA’s assertion in its Proposed Rule that the ten drugs most prescribed for children all lack adequate pediatric labeling is simply inaccurate. See 62 Fed. Reg. at 43,900. As the Pharmaceutical Manufacturers Association of America has explained: five of the ten drugs cited by FDA already contain pediatric labeling; one is in the midst of FDA’s approval process; one does not have labeling, but extensive dosage information about it is available in pediatric and standard medical texts; one does not have an NDA on file to amend because it has an exemption under the grandfather clause; and one states on its label that it is not approved for diaper dermatitis. PhRMA Comments, *supra* note 59, at 4-5.



Goldschmidt, 645 F.2d 1309, 1317 (8th Cir. 1981) (same). Instead, FDA relies on nothing more than a handful of anecdotes documenting adverse reactions in children from off-label drug uses. See 62 Fed. Reg. at 43,901.

Adverse drug reactions, however, regularly occur from on-label uses as well. Thus, identification of a few adverse reactions from off-label drug uses in pediatric populations is an insufficient justification for the Rule. Rather, FDA must establish that a significant number of those reactions could have been prevented if those same products had been tested and approved for use in children, taking into account, of course, the likelihood of adverse drug reactions that might occur as a result of the clinical testing itself.

Even if the articles describing these scattered instances of adverse reactions did suggest that pediatric testing of an unapproved product might lead to fewer adverse drug reactions than would waiting to prescribe that product in children until after it has been approved as safe and effective for adults, isolated anecdotes cannot suffice to support the sweeping regulations embodied in the Pediatric Rule. See, e.g., 5 U.S.C. § 557(c) (1994) ("All decisions, including initial, recommended, and tentative decisions . . . shall include a statement of . . . findings and conclusions, and the reasons or basis therefor, on all the material issues of fact, law, or discretion presented on the record . . ."); State Farm, 463 U.S. at 43 (holding that "agency must examine the relevant data and articulate a satisfactory explanation for its action"); Burlington Truck Lines, Inc. v. United States, 371 U.S. 156, 167 (1962) (rejecting agency decision where "[t]here are no

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<sup>76</sup> See Beck & Azari, *supra* note 4, at 82 (emphasizing that "previously unknown safety concerns can arise with labeled as well as unlabeled indications").

findings and no analysis . . . to justify the choice made[] [and] no indication of the basis on which the Commission exercised its expert discretion")."

In sum, the Pediatric Rule is not only inconsistent with FDAMA, it is also bad policy. Far from streamlining and accelerating the drug approval process, the Rule complicates and hinders that process. Moreover, instead of encouraging manufacturers to seek approval for off-label uses of a drug on a voluntary basis, the Rule forces manufacturers to seek approval for uses of their product that they did not intend to pursue. FDA should effectuate the goal of bringing pediatric indications on-label through the incentive scheme established by Congress in FDAMA.

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To the extent that there remains some lingering concern over the availability and safety of current pediatric treatments, Congress has already addressed the problem by enacting the Pediatric Exclusivity provisions in FDAMA. FDA cannot override Congress's policy choice concerning the most appropriate means of addressing this issue. See supra pp. A-10 to A-12.

## APPENDIX B:

**THE PEDIATRIC RULE CONTRAVENES THE LONG-STANDING VIEW OF CONGRESS, THE COURTS, AND FDA THAT FDA'S AUTHORITY IS LIMITED TO "INTENDED," OR CLAIMED, USES OF DRUGS AND DOES NOT ENCOMPASS USES THAT FDA CONSIDERS "FORESEEABLE."**

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## APPENDIX B:

### **THE PEDIATRIC RULE CONTRAVENES THE LONG-STANDING VIEW OF CONGRESS, THE COURTS, AND FDA THAT FDA'S AUTHORITY IS LIMITED TO "INTENDED," OR CLAIMED, USES OF DRUGS AND DOES NOT ENCOMPASS USES THAT FDA CONSIDERS "FORESEEABLE."**

Since the 1906 origins of federal food and drug law to the present, the "intended uses" of a product universally have been understood to mean those uses set forth by the manufacturer in the product's labeling. Throughout that ninety-three year history, Congress has used the term of art "intended use" to determine whether an article is a drug or device at all, whether a product requires premarket review and approval, what premarket testing and evidence are required, what standards and procedures govern any review, and what must and must not appear in a product's labeling. In crafting the term "intended use," Congress accommodated both FDA's power of premarket review and the freedom of physicians to practice medicine in accordance with their professional judgment.

The federal food and drug regulatory structure that Congress has erected clearly demonstrates that manufacturers determine the "intended uses" of their products through their labeling claims. It also shows that a use does not become "intended" merely because that use is foreseeable or desired. Indeed, important provisions of the Food, Drug, and Cosmetic Act ("FDCA") cannot operate if all foreseeable uses are deemed "intended" and therefore within FDA's jurisdiction.

Ample judicial authority confirms that the "intended uses" of a drug are limited to uses claimed by the manufacturer and do not include uses that are foreseeable but not claimed by the manufacturer. Likewise, as Congress shaped the FDCA, FDA repeatedly advised that its regulatory authority extended only to "intended uses," which derived from manufacturer claims.

and that it could not regulate other off-label uses. FDA's actual practices in enforcing the food and drug laws confirm this limitation on its authority.

Despite the settled understanding that FDA may legitimately regulate only the "intended uses" – i.e., claimed uses – of a drug, FDA, in promulgating the Pediatric Rule, now asserts that its regulatory authority encompasses foreseeable uses as well. See 63 Fed. Reg. at 66,657-58 (asserting that "[i]ntended uses" encompass more than the uses explicitly included in the manufacturer's proposed labeling" but also include "actual uses of the drug of which the manufacturer has, or should have, notice, even if those uses are not promoted by the manufacturer"). FDA further asserts that those "foreseeable uses" purportedly subject to its authority include pediatric uses of new and marketed drugs and biologics previously approved only for adult use:

Pediatric patients are a significant subpopulation, affected by many of the same diseases as adults, and are foreseeable users of new drugs and biologics.

Id. at 66,645; see also id. at 66,653 ("FDA believes that it has ample authority to require pediatric studies of marketed drugs and biologics . . .").<sup>1</sup>

In an even bolder attempt to expand its power beyond claimed uses, FDA also argues that a foreseeable use remains foreseeable – and therefore purportedly subject to FDA's jurisdiction – "even where such use is not expressly recommended or is even disclaimed" – as are all pediatric

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<sup>1</sup> The Department of Health, Education, and Welfare, the predecessor to FDA's current parent agency, has condemned this practice. In a 1977 report, the Department stated that it "would be inappropriate for FDA to require a drug sponsor to investigate new uses for a marketed drug or the use of the drug in different patient populations, unless there is reliable evidence of widespread unapproved use of the drug. If FDA wishes to explore new or different uses for an approved drug, it might consider financing the studies itself." Department of Health, Education, and Welfare, Final Report: Review Panel on New Drug Regulation, at 97 (1977).

uses of adult-use drugs. Id. at 66,658; 21 C.F.R. § 201.57(f)(9)(v) (requiring manufacturer to disclaim pediatric uses of adult-use drugs). FDA even applies its “foreseeability” theory to drugs that have not yet been marketed and therefore have never actually been used in pediatric populations. For these drugs, FDA purports to establish a per se legal presumption that their use in pediatric populations is foreseeable solely because the diseases treated by those proposed drugs occur in pediatric populations.

As Congress, the courts, and even prior FDA statements and practices have confirmed for years, however, Congress has not given FDA such sweeping powers to treat foreseeable uses as “intended uses,” particularly where disclaimed. Rather, as demonstrated below, Congress has limited FDA to ensuring that the claims made in a drug’s labeling are true. In light of this well-settled understanding, FDA cannot regulate off-label pediatric uses in the manner proposed by the Pediatric Rule.

**I. THE LEGISLATIVE DEVELOPMENT OF THE “INTENDED USE” CONCEPT IN THE FDCA CONFIRMS THAT CONGRESS INTENDED TO CONFINE FDA’S REGULATORY AUTHORITY TO CLAIMED USES OF A PRODUCT.**

Since the enactment of the first federal food and drug law nearly a century ago, Congress has consistently limited FDA’s drug regulatory authority to “intended uses” – i.e., uses claimed by the manufacturer. In light of this unambiguous history, FDA’s assertion of authority to require a manufacturer to study uses of a drug that a manufacturer does not claim but that FDA deems to be foreseeable – in this case pediatric uses – is untenable.

In 1906, Congress enacted the Pure Food and Drugs Act, the first national effort to protect the public health by regulating drugs. Pub. L. No. 59-384, 34 Stat. 768 (1906). The Act defined “drugs” as (1) products listed in the United States Pharmacopoeia or National Formulary

or (2) "any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals." *Id.* § 6, 34 Stat. at 769. The 1906 Act prohibited the sale only of "adulterated" and "misbranded" products, which were products whose actual composition deviated from the composition specified in the label. *Id.* §§ 8, 10, 34 Stat. at 770-71. As long as the product's label accurately reflected the product's composition, the product fell outside the 1906 Act's regulatory scope. Thus, manufacturers could determine the "intent" necessary to bring a non-listed product within the 1906 Act's regulatory scope solely by the claims that they made in the product's label. Indeed, if unlabeled, but foreseeable, uses of a product to cure, mitigate, or prevent disease sufficed to establish the requisite "intent" to categorize the product as a drug, then many "drugs" anomalously could not be regulated under the Act, which only condemned products as "adulterated" or "misbranded" on the basis of their label claims. *See id.*

In 1938, Congress enacted the Food, Drug, and Cosmetic Act ("FDCA"), Pub. L. No. 75-717, 52 Stat. 1040 (1938), which made a number of key changes to the 1906 Act but did not alter the claims-based nature of the "intended use" concept. Most significantly, Congress required, for the first time, that before introduction to the market for commercial distribution, manufacturers of new drugs must affirmatively demonstrate that the drug is safe "for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." *Id.* § 505(d)(1), 52 Stat. at 1052 (codified as amended at 21 U.S.C. § 355(d)(1)).<sup>2</sup>

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<sup>2</sup> "Labeling" was defined to include "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." Pub. L. No. 75-717, § 201(m), 52 Stat. at 1041 (codified as amended at 21 U.S.C. § 321(m) (1994)).

As this last change illustrates, Congress's limitation on the scope of FDA premarket safety review to claims in the manufacturer's labeling demonstrated Congress's understanding that FDA could regulate only the uses which a manufacturer claimed in its labeling -- i.e., the product's "intended uses." Congress did not extend FDA authority to unclaimed uses of a product, no matter how foreseeable. The accompanying Senate Report on one of the bills that led to the 1938 Act explicitly recognized this vital link between manufacturer claims and federal regulatory jurisdiction by providing that:

The use to which a product is to be put will determine the category into which it will fall. . . . The manufacturer of the article through his representations in connection with its sale can determine the use to which the article is to be put.

S. Rep. No. 73-493, at 2-3 (1934). FDA, as well as numerous courts, have relied on this statement. See, e.g., Labeling: General Requirements for Health Claims for Food, 56 Fed. Reg. 60,537, 60,546 (1991); ASH v. Harris, 655 F.2d 236, 238-39 (D.C. Cir. 1980); United States v. An Article . . . "Sudden Change", 409 F.2d 734, 739 n.3 (2d Cir. 1969).<sup>3</sup>

In 1962, Congress again amended the food and drug laws. This time Congress required drug manufacturers seeking approval to demonstrate that their proposed product was not only safe but also effective for each "use . . . prescribed, recommended, or suggested in the labeling thereof." Pub. L. No. 87-781, § 102(c), 76 Stat. 780, 781-82 (1962) (codified at 21 U.S.C. § 355(d)(5) ("1962 Drug Amendments")); see also S. Rep. No. 87-1744, pt. 2, at 5 (1962) ("[A]ll

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<sup>3</sup> FDA's reliance on its regulation defining "intended use" in support of its argument that "intended uses" include common or foreseeable uses is without merit. See 21 C.F.R. § 201.5 (1999) (defining "intended use" for a drug); id. § 801.5 (defining "intended use" for a device). Both regulations distinguish between intended uses and common uses. This reading is confirmed by the text of the FDCA, which requires that a drug or device be safe and effective only for labeled uses. See 21 U.S.C. §§ 355(d), 360c, 360e (1994 & Supp. III 1997). It would be absurd to define "intended use" as a use that the statute does not require to be safe and effective.



claims for effectiveness, whether made initially in a new-drug application or at any time thereafter, must be supported by 'substantial evidence' . . . .").

The legislative history surrounding the enactment of the 1962 Drug Amendments demonstrates that both Congress and FDA used the terms "claimed use," "intended use," and "conditions prescribed, recommended, or suggested in the labeling" interchangeably. For example, the Senate Committee Report described the bill<sup>4</sup> as requiring "a premarketing showing that all new drugs are effective – as well as safe – for their intended uses." S. Rep. No. 87-1744, pt. 1, at 8 (1962), reprinted in 1962 U.S.C.C.A.N. 2884, 2884. The House Committee Report likewise stated that if "the drug is generally recognized by experts to be effective for the conditions for which it is intended, it is not a new drug." H.R. Rep. No. 87-2464, at 8 (1962).

Similarly, the Secretary of Health, Education, and Welfare ("HEW"), FDA's parent agency, testified during hearings for the House version of the bill that it would operate "by requiring that new drugs be shown effective for their intended uses, as well as safe, before they are marketed." See Drug Industry Act of 1962: Hearings Before the House Comm. on Interstate and Foreign Commerce, 87th Cong. 61 (1962) (statement of HEW Secretary Ribicoff). The HEW Secretary made a similar comment with respect to the Senate version of the bill. Drug Industry Antitrust Act: Hearings Before the Subcomm. on Antitrust and Monopoly of the Senate Comm. on the Judiciary, 87th Cong. 2583 (1961) (statement of HEW Secretary Ribicoff) (testifying that HEW supported the legislation because "[t]he manufacturer should satisfy the

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<sup>4</sup> Both the Senate and the House versions of the bill contained the ultimately enacted requirement that a drug be found to be effective for use "under the conditions prescribed, recommended, or suggested in the labeling." See S. 1552, 87th Cong. § 4(a)(9) (as introduced) (1961); H.R. 11581, 87th Cong. Title I, Part A, § 102(d) (as reported) (1962).

FDA that his product is effective for the purposes claimed before it is marketed"). In short, there was unanimity that "claimed use," "intended use," and "use under the conditions prescribed, recommended, or suggested in the labeling" were synonymous terms.

The Drug Price Competition and Patent Term Restoration Act of 1984 further illustrates the critical link that exists between a manufacturer's claims set forth in a product's labeling and the product's "intended uses." In that Act, Congress authorized an "abbreviated new drug application" ("ANDA") procedure by which the manufacturer of a generic version of a previously approved "pioneer" drug can avoid the expensive and time-consuming testing and review required to obtain approval of a standard NDA). Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355(j) (1994 & Supp. III 1997)).

In substance, the 1984 Act provides that if the ANDA applicant shows that a drug is "bioequivalent" to (the same in the body as) a pioneer drug that already has been approved, and if "the labeling proposed for the new drug is the same as the labeling approved for the listed drug," FDA must approve the drug without requiring additional clinical testing. 21 U.S.C. § 355(j)(2)(A)(iv), (4)(F). In other words – and contrary to FDA's present position with respect to the Pediatric Rule – FDA could not require ANDA applicants to study or claim foreseeable, off-label uses as a prerequisite to approval of the follow-on generic product. Rather, an ANDA could claim only those conditions of use that previously had been approved in a pioneer drug application. See H.R. Rep. No. 98-857, pt. 1, at 21 (1984), reprinted in 1984 U.S.C.C.A.N.

2647. 2654 ("[A]n ANDA may not be considered for a condition of use that has not previously been approved for the listed drug." ).<sup>5</sup>

Notably, the 1984 amendments retained the FDCA's requirement that FDA approve each intended use before a drug is distributed. See 21 U.S.C. § 355(d). Thus, because (1) generic drug manufacturers could not seek approval for foreseeable off-label uses of the pioneer product on the basis of an ANDA, and (2) approval of an ANDA signifies that the generic drug is safe and effective for each of its "intended uses," the 1984 amendments establish that Congress did not consider foreseeable off-label uses of the pioneer product to be "intended uses" of the generic follow-on for which approval was required.

Most recently, FDA asserted the authority to regulate off-label uses of devices in connection with Congress's 1997 enactment of FDAMA. Congress, however, rejected FDA's assertion of jurisdiction and refused to make such uses "intended uses" for which manufacturers were required to establish the safety and effectiveness of the product. See, e.g., S. Rep. No. 105-43, at 27 ("This section includes two provisions that express the committee's specific intention to limit FDA's review of premarket submissions to the proposed labeling before the agency."). Instead, it temporarily authorized FDA, in reviewing a submission under 21 U.S.C. § 360(k), to require a manufacturer to include in the labeling of its device a statement of "appropriate information" about an unclaimed use if – but only if – FDA expressly determined in writing that there is "a reasonable likelihood" that the device will be employed for that unclaimed use and

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<sup>5</sup> This process was analogous to provisions in the earlier enacted 1976 Medical Device Amendments, which allowed FDA to give clearance to "substantially equivalent" follow-on devices as long as they claimed only the "intended uses" approved for the pre-existing devices that they imitated. See Pub. L. No. 94-295, 90 Stat. 539 (1976) (codified as amended at 21 U.S.C. § 360c(f)(3), (i)(1)(A)).

that "that use causes harm." Id. § 360c(i)(1)(E)(i) (1994 & Supp. III 1997) (substantial equivalence); id. § 360c(i)(1)(E)(iv) (five-year sunset on FDA authority). This limited provision did not authorize FDA to require manufacturers to conduct additional clinical studies for the unclaimed use in order to demonstrate the safety and effectiveness of that use. Rather, it required manufacturers to submit previously known information concerning that use, including a statement that there is insufficient information to justify the use. Thus, far from converting the unclaimed use into an "intended use," Congress once again confirmed that "[a]ny determination by the Secretary of the intended use of a device shall be based upon the proposed labeling." Id. § 360c(i)(1)(E)(i); accord S. Rep. No. 105-43, at 27.

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In sum, the history of federal food and drug legislation demonstrates that Congress only considers claimed uses by the manufacturer – and not foreseeable uses – to be "intended uses" for which safety and effectiveness data must be submitted. Thus, unless a manufacturer claims that a drug may be used for pediatric purposes, FDA may not regulate such uses as "foreseeable."

## **II. THE COURTS HAVE CONSISTENTLY CONFIRMED THAT COMMUNICATED MANUFACTURER CLAIMS DETERMINE "INTENDED USE."**

Ample judicial authority supports the essential link between manufacturer claims and "intended uses" and denies FDA the right to deem foreseeable uses as "intended." Indeed, the courts "have always read the . . . statutory definitions employing the term 'intended' to refer to specific marketing representations." American Health Prods. Co. v. Hayes, 574 F. Supp. 1498, 1505 (S.D.N.Y. 1983), aff'd on other grounds, 744 F.2d 912 (2d Cir. 1984). As early as Bradley v. United States, 264 F. 79 (5th Cir. 1920), "intended use" was based upon claims, not actual or foreseeable effects. In 1953, the Second Circuit held that claims were essential to establish an

"intended use." See FTC v. Liggett & Myers Tobacco Co., 203 F.2d 955, 955 (2d Cir. 1953) (per curiam), aff'd 108 F. Supp. 573 (S.D.N.Y. 1952)." "The real test is how was this product being sold?" United States v. Nutrition Serv., Inc., 227 F. Supp. 375, 386 (W.D. Pa. 1964), aff'd, 347 F.2d 233 (3d Cir. 1965).

The District of Columbia District Court and Circuit Court of Appeals also have rejected FDA's attempt to regulate drugs beyond their labeled uses. In American Pharmaceutical Ass'n v. Weinberger, FDA asserted the authority to impose controls on distribution for methadone, which it had found to be safe for its labeled use but which it argued was unsafe when used off-label. 377 F. Supp. 824, 828 (D.D.C. 1974) (noting FDA's argument that drug must be "safe" not only for labeled uses but also for possible misuses), aff'd sub nom. American Pharm. Ass'n v. Mathews, 530 F.2d 1054, 1055 (D.C. Cir. 1976) (McGowan, J., concurring) ("The FDA contends that where there exists a documented pattern of drug misuse contrary to the intended uses specified in the labeling, the drug is unsafe for approval [absent further FDA regulation]."). The court rejected as outside of FDA's statutory authority FDA's attempt to regulate methadone in this manner. See American Pharm. Ass'n, 377 F. Supp. at 827. The appellate court affirmed per curiam "on the basis of the opinion of the District Court." American Pharm. Ass'n, 530 F.2d at 1054; see also id. at 1055 (McGowan, J., concurring) (agreeing with district court that "methadone is safe for its intended use notwithstanding the possibility that it will be employed in unintended fashions").

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<sup>6</sup> The FDCA's definition of "drug" had been imported wholesale into the FTC Act as part of a provision dividing responsibility between FTC and FDA. Compare 21 U.S.C. § 321(g)(1) (1994) with 15 U.S.C. § 55(c) (1994).

In 1980, the D.C. Circuit again confirmed that FDA's regulatory authority is limited by manufacturer claims. See ASH, 655 F.2d at 238-39. Specifically, the court held that:

the crux of FDA jurisdiction [lies] in manufacturers' representations as revelatory of their intent. . . . "The manufacturer of the article, through his representations in connection with its sale, can determine the use to which the article is to be put . . ." Such an understanding has now been accepted as a matter of statutory interpretation.

Id. (quoting S. Rep. No. 73-493, at 2-3 (1934)).

That "accepted" statutory construction was reaffirmed more recently in United States v. Articles of Drug for Veterinary Use, 50 F.3d 497 (8th Cir. 1995). There, the court held that if a manufacturer's written materials were not communicated to purchasers, they were not relevant to the issue of intended use. See id. at 499-500. In other words, although undistributed promotional material might show a manufacturer's knowledge, foreseeability, and desire, only communication to the market creates an "intended use."<sup>8</sup>

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Because FDA had shown no inclination to change its statutory interpretation at that time, the court noted in dictum that it was not deciding whether such a change would be possible. ASH, 655 F.2d at 242 n.10.

Courts have repeatedly relied on manufacturers' explicit claims regarding their products to rule that the products are drugs. See, e.g., Seven Cases of Eckman's Alterative v. United States, 239 U.S. 510 (1916) (treating product represented as a preventative cure for throat and lung diseases as a drug); United States v. Undetermined Quantities of Bottles, 22 F.3d 235 (10th Cir. 1994) (finding product to be a drug based upon manufacturer's claims that product would eliminate bad odors in animals); United States v. Storage Spaces Designated Nos. "8" & "49", 777 F.2d 1363 (9th Cir. 1985) (holding cocaine substitutes to be drugs because manufacturers promoted their products as cocaine substitutes); United States v. Guardian Chem. Corp., 410 F.2d 157 (2d Cir. 1969) (noting that promotional literature making drug claims would be sufficient to regulate product as a drug); Gray v. United States, 174 F.2d 919 (8th Cir. 1949) (finding that substance was a drug based on representation that product would "correct ulcers"); United States v. Research Labs., Inc., 126 F.2d 42 (9th Cir. 1942) (holding that product was a drug because it was represented as a treatment for arthritis); United States v. Kasz Enters., 855 F. Supp. 534 (D.R.I. 1994) (finding that hair products were drugs because manufacturer marketed the products as hair growth stimulation and hair loss prevention products); United States v. Vital

(Continued...)

In sum, judicial authority confirms that only claimed uses qualify as "intended uses," and those claimed uses therefore delimit FDA's authority.

**III. FDA HAS CONSISTENTLY AND REPEATEDLY TOLD CONGRESS THAT THE ONLY "INTENDED USES" OF A PRODUCT SUBJECT TO ITS REGULATORY AUTHORITY WERE USES THAT A MANUFACTURER CHOSE TO INCLUDE IN THE LABELING.**

FDA itself has repeatedly advised Congress and others that only manufacturer statements establish "intended use." The issue often arose with respect to tobacco, and FDA's statements in that regard are frequent and unequivocal. The Department of Justice accurately summarized FDA's historical position in a 1980 brief defending FDA's conclusion that it lacked jurisdiction to regulate cigarettes:

In the 73 years since the enactment of the original Food and Drug Act, and in the 41 years since the promulgation of the modern Food, Drug, and Cosmetic Act, the FDA has repeatedly informed Congress that cigarettes are beyond the scope of the statute absent health claims . . . .

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(... Continued)

Health Prods., Ltd., 786 F. Supp. 761 (E.D. Wis.) (concluding that hydrogen peroxide solutions were drugs based on manufacturer claims about the solutions), aff'd, 985 F.2d 563 (7th Cir. 1992) (table); United States v. Undetermined Quantities of "Cal-Ban 3000 \* \* \*", 776 F. Supp. 249 (E.D.N.C. 1991) (holding that product marketed to public for purpose of weight reduction, appetite suppression, and prevention of colon cancer was a drug); United States v. Undetermined Quantities of an Article of Drug Labeled as "Exachol", 716 F. Supp. 787 (S.D.N.Y. 1989) (finding that product was a drug because manufacturer claimed therapeutic effect on the product's label); United States v. Articles of Drug, Foods Plus, Inc., 239 F. Supp. 465 (D.N.J.) (concluding that product was a drug based on manufacturer's representation that it would cure a wide variety of ills), remanded on other grounds, 362 F.2d 923 (3d Cir. 1966); United States v. 250 Jars, etc., of U.S. Fancy Pure Honey, 218 F. Supp. 208 (E.D. Mich.), aff'd, 344 F.2d 288 (6th Cir. 1965) (concluding that product was a drug based upon representation that product would cure a wide variety of ills); United States v. 3 Cartons, 132 F. Supp. 569 (S.D. Cal. 1952) (concluding that products at issue were drugs based on manufacturer representations).

[Even before the 1950s, there are many examples] of [FDA's] interpretation that cigarettes and related tobacco products are not a "drug" under the Act except when there are health claims, including correspondence between the agency and members of Congress. . . . These records, including correspondence dating from at least as early as 1940, show that the Commissioner's interpretation was in accordance with the contemporaneous construction of the 1938 Act by the persons charged with its administration.<sup>9</sup>

FDA's admissions are not limited to the tobacco context but extend to the pharmaceutical context as well. For example, in 1967, former FDA official John Jennings acknowledged that "[i]t is the manufacturer who chooses the indications to be investigated and determines the dosage level for which he will seek FDA approval"; FDA's limited role is "to decide that proposed usages and levels are both safe and effective, based on the data submitted by the manufacturer."<sup>10</sup> Similarly, a former Bureau of Drugs Director conceded that FDA "is neither authorized or equipped to carry out studies of its own, nor can it control a firm's decision about the investigation or production of one of its drugs." Competitive Problems in the Drug Industry:

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<sup>9</sup> Brief for Appellees, at 14-15, 22 n.19, ASH v. Harris, 655 F.2d 236 (D.C. Cir. 1980) (No. 79-1397); see Bureau of Chemistry, United States Department of Agriculture, Service and Regulatory Announcements No. 13, The Status of Tobacco and Its Preparations Under the Food and Drugs Act 24 (1914) ("[T]obacco and its preparations, when labeled . . . to indicate their use for the cure, mitigation, or prevention of disease, are drugs within the meaning of the act and, as such, are subject to [its] provisions. . . . [T]obacco and its preparations which are not so labeled and are used for smoking or chewing or as snuff and not for medicinal purposes are not subject to the provisions of the act."); May 24, 1963 FDA Bureau of Enforcement Guideline, reprinted in Public Health Cigarette Amendments of 1971: Hearings Before the Consumer Subcomm. of the Senate Comm. on Commerce, 92d Cong. 240 (1972) ("The statutory basis for the exclusion of tobacco products from FDA's jurisdiction is the fact that tobacco marketed for chewing or smoking[,] without accompanying therapeutic claims, does not meet the definitions . . . for food, drug, device or cosmetic."); Cigarette Labeling and Advertising - 1965: Hearings Before the House Comm. on Interstate and Foreign Commerce, 89th Cong. 193 (1965) (FDA Commissioner Rankin's testimony admitting that FDA "has no jurisdiction under the Food, Drug, and Cosmetic Act over tobacco, unless it bears drug claims").

<sup>10</sup> John Jennings, The Rx Label: Basis for All Prescribing Information, FDA Papers, Nov. 1967, at 14-15.



Hearings Before the Subcomm. on Monopoly of the Senate Select Comm. on Small Business.

93d Cong. 9406 (1973) (statement of Bureau of Drugs Director Henry E. Simmons).

More recently, former FDA official Stuart L. Nightingale acknowledged that "[w]hile the FDA can and does encourage the submission of supplemental NDAs for unlabeled uses, the decision about whether or not, and when, to submit such an application is the decision of the sponsor."<sup>11</sup> A contemporaneous trade press article confirmed the official's conclusion.

Perhaps former FDA official J. Richard Crout most aptly summarized the reason why FDA's current attempt to regulate allegedly foreseeable off-label uses is improper when he stated that:

it is essential that those of us in regulatory agencies and in the legal profession not take offense at drug usage outside the package insert merely because it is occurring. We must understand how our drug labeling system works and recognize that such usage will occur as a necessary part of the practice of good medicine; and the more current the physician is in his practice, the more often it will occur. Understanding this, we in government and in law cannot threaten to use the package insert as a tight regulatory standard for the practice of medicine. Such a threat would do nothing beneficial for patient care and would serve only to antagonize the medical profession for no good purpose.<sup>13</sup>

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In sum, the evidence is overwhelming that Congress, the courts, and FDA have, for nearly a century, considered "intended uses" to be limited to claimed uses. FDA's recently

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<sup>11</sup> Stuart L. Nightingale, Unlabeled Uses of Approved Drugs, 26 Drug Information J. 141, 142 (1992) (originally presented at the Drug Information Workshop, Oct. 1990).

<sup>12</sup> See The FDA and Off-Label Drug Use, U.S. Reg. Rep., June 1989, at 2-3 ("Obviously, drug manufacturers are under no legal or regulatory obligation to discourage off-label drug use or to legitimize unapproved indications by pursuing FDA approval.").

<sup>13</sup> J. Richard Crout, In Praise of the Lowly Package Insert, 29 Food Drug Cosm. L.J. 139, 143-44 (1974).

promulgated Pediatric Rule is inconsistent with this uniform interpretation. Indeed, the Pediatric Rule is an even more dramatic departure from this well-settled understanding because it not only treats "foreseeable uses" as "intended uses," but it also purports to create a per se legal presumption that pediatric drug uses are "foreseeable" based on nothing more than the occurrence in pediatric patients of the disease that the drug treats. FDA applies this presumption even where the manufacturer expressly disclaims use of a drug in pediatric populations, and even where the drug has never actually been used in pediatric populations. In light of FDA's departure from the well-settled and universally understood limits on its authority – a departure that far exceeds even FDA's position in the tobacco dispute in which FDA is currently embroiled<sup>14</sup> – the regulations comprising the Rule should be revoked.

**IV. IF FAITHFULLY APPLIED, THE FORESEEABILITY THEORY UNDERLYING THE PEDIATRIC RULE WOULD HINDER THE APPROVAL OF BOTH PIONEER AND GENERIC FOLLOW-ON PRODUCTS AND CAUSE AN OVERWHELMING NUMBER OF MARKETED PRODUCTS TO BE DECLARED MISBRANDED.**

**A. The Approval Process For Pioneer Products Would Be Hindered.**

Carried to its logical conclusion, FDA's foreseeability theory underlying the Pediatric Rule would seriously delay and complicate the process of obtaining FDA approval for pioneer drugs and devices.

Many drugs and devices originate or are first approved and used outside the United States. By the time FDA approval is sought, a range of uses may be documented in the literature. Important uses of a new drug or device also may emerge during the often lengthy period of FDA

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<sup>14</sup> The Supreme Court is currently considering FDA's new interpretation of intended use and its concomitant assertion of jurisdiction over tobacco products in FDA v. Brown & Williamson Tobacco Co., 153 F.3d 155 (4th Cir. 1998), cert. granted, 119 S. Ct. 1495 (1999).

review. See United States v. Algon Chem. Inc., 879 F.2d 1154, 1163 (3d Cir. 1989) ("New uses for drugs are often discovered after FDA approves the package inserts that explain a drug's approved uses."). Some uses, however, are far more difficult to test than others. Others may not appear economically important enough to justify the considerable expense of separate testing. Under 21 U.S.C. § 355(d), FDA cannot approve a drug unless all of its "intended" uses are proved safe and effective. The same is true for devices. See 21 U.S.C. § 360e(d)(2) (1994 & Supp. III 1997) (requiring devices to be safe and effective for their "intended" uses). Thus, the definition of an "intended use" drastically impacts the approval process for a new drug or device.

Under the conventional view, the manufacturer determines the intended uses of the article by what is claimed in the labeling. A manufacturer with limited funding can thus target key uses for initial approval, bringing the drug or device quickly to the market, even though other foreseeable uses may merit later supplemental testing and approval to expand the scope of a manufacturer's promotional claims about the product. So long as the labeling determines the intended uses, however, none of the emerging new uses can delay or complicate approval of the original application. This long-standing view of "intended uses" enables manufacturers to place valuable new drug treatments into the hands of patients who need them in an efficient and expeditious manner.

Under FDA's novel position that it has the power to define foreseeable uses as intended uses, manufacturers would be denied the choice to market a product for limited uses only. Because manufacturers must establish that all "intended uses" are safe and effective, no drug or

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<sup>15</sup> See Michael P. VanHuysen, Note, Reform of the New Drug Approval Process, 49 Admin. L. Rev. 477, 488-89 (1997).

device approval could be granted until every foreseeable use had been tested and supported.

Thus, the manufacturer would have to make an all-or-nothing choice: either test and obtain approval for all foreseeable uses as defined by FDA, or forego FDA approval entirely.<sup>16</sup>

Even for a manufacturer opting to go forward and subject itself to this onerous scheme, FDA could force it repeatedly to revise its labeling and supplement its submissions, conducting whatever further tests that FDA believes are needed to satisfy FDA's ever evolving and expanding definition of a product's "foreseeable uses." At a minimum, this would cause substantial delay in obtaining FDA approval for the originally specified uses. At worst, the process could continue indefinitely until the manufacturer runs out of resources. Ironically, the more useful the new product turns out to be, the longer it would take to get it approved for any use at all. In short, consistent application of FDA's foreseeability theory would seriously obstruct a drug innovator's ability to place valuable new treatments into the hands of ailing patients.

#### **B. The Approval Process For Follow-On Products Would Be Thwarted.**

Consistent application of FDA's foreseeability theory would create similar problems for follow-on products. The ANDA process to obtain expedited approval of a generic drug, see 21

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<sup>16</sup> The problem does not arise solely from a manufacturer's actions. Actions of the medical profession completely independent of the manufacturer can make a use foreseeable. For example, a physician, in the course of practicing medicine, may try a drug or device for a new use in a few patients and report the experience at a professional conference or in a medical journal. Other physicians may try the new use. Their success may lead to further communications, perhaps on the Internet. Very soon, the use becomes foreseeable. But all "intended uses" must be approved by FDA and described in a product's FDA-approved labeling. See 21 U.S.C. §§ 355(a), 352(f) (1994); 21 C.F.R. § 310.3(h)(4) (1999). If every foreseeable use were an intended use, then every drug and device with a foreseeable off-label use created in the manner just described is being marketed unlawfully.

U.S.C. § 355(j), and the substantial equivalence clearance process for follow-on devices. see id. §§ 360(k), 360c(f), (i) (1994 & Supp. III 1997), limit the intended uses that may be approved. See supra pp. B-7 to B-9. Specifically, the labeling of a generic drug seeking ANDA approval must be substantially identical to that of the pioneer. See id. § 355(j)(2)(A)(v), (4)(G); 21 C.F.R. § 314.94(a)(8) (1999). Likewise, a follow-on device must be “substantially equivalent” to the predicate device, see 21 U.S.C. § 360c(f)(1)(A), and must have the same “intended use.” see id. § 360c(i)(1)(A); 21 C.F.R. § 807.92(a)(5) (1999). If those requirements are not met, FDA must deny approval or clearance. See 21 U.S.C. §§ 355(j)(4)(B), 360(n) (Supp. III 1997). In other words, follow-on products are prohibited from having any intended uses or indications that were not approved for the pioneer product and supported by its labeling.

But circumstances at the time that a manufacturer submits a follow-on application – generally at or near the end of the period of patent exclusivity – may be very different from those when the pioneer product entered the market. The pioneer will have been on the market for some time, and important off-label uses may have arisen from the medical community’s experience with the product.<sup>17</sup> Indeed, those may be the predominant continuing uses, as other new products may have rendered the original “intended uses” largely obsolete.

No impediments to approval arise under the understanding of “intended use” that existed before FDA’s pediatric rulemaking. As long as the labeling of the follow-on product did not claim an off-label use, that use was not an “intended use” subject to FDA approval – regardless of how foreseeable, common, and desired it may have been. Thus, the follow-on manufacturer

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<sup>17</sup> One such situation is described in In re Orthopedic Bone Screw Products Liability Litigation, 159 F.3d 817 (3d Cir. 1998), pet. for cert. filed, 67 U.S.L.W. 3684 (U.S. May 3, 1999) (No. 98-1768).

simply would employ the same labeling claims as the original manufacturer and obtain expedited approval, providing the competition that Congress sought to foster in enacting the follow-on drug and device approval provisions.

By contrast, under FDA's new theory, foreseeable, common, or desired off-label uses are "intended uses" regardless of what the manufacturer claims. A dilemma results. FDA cannot approve a drug or device until all of its intended uses are supported by its labeling. See 21 U.S.C. § 352(f)(1); 21 C.F.R. §§ 201.5, 314.94(a)(8) (drugs); 21 U.S.C. §§ 360(k), 360c(i); 21 C.F.R. § 801.5 (devices). Yet FDA cannot approve the follow-on product if its labeled uses include some uses not claimed in the labeling for the pioneer product. See 21 U.S.C. § 355(j)(2)(A)(v), (4)(G) (drugs); id. §§ 360(k), 360c(i); 21 C.F.R. § 807.92(a)(5) (devices); see also 21 U.S.C. § 360c(i)(1)(E)(i) (substantial equivalence for devices). There is no exit from the dilemma. The manufacturer of a generic drug could incur the expense and delay of a full new drug application to obtain approval for these foreseeable, but unclaimed, uses. Such a strategy, however, would sacrifice the expedited approval process altogether. Thus, if applied faithfully, FDA's new theory would thwart Congress's goal of increased competition, jeopardizing the whole system for approving generic drugs and follow-on devices.

### **C. Marketed Products Would Be Misbranded.**

Faithful application of FDA's new theory that foreseeable uses are "intended" – and therefore subject to FDA's jurisdiction – would also wreak havoc among drugs and devices already on the market. Drugs and devices are misbranded and cannot be sold unless all of their intended uses have been approved by FDA and are supported by the labeling. See 21 U.S.C. §§ 355(a), 352(f)(1). Taken seriously, FDA's theory would mean that each time an off-label use

for an approved product becomes foreseeable, the product would become misbranded (because its labeling would not support all of its intended uses), and the product would have to be withdrawn from the market.

**D. Serious Issues Would Arise Regardless Of FDA's Enforcement Posture.**

To avert these difficulties, FDA might invoke "enforcement discretion" to approve or allow the continued marketing of drugs and devices with unapproved "intended uses." Such a regime would be unlawful. See Heckler v. Cheney, 470 U.S. 821, 833-34 (1985) (holding that agency cannot suspend a statute).

Even if those difficulties could be surmounted, the FDCA has important effects that are not subject to FDA discretion. For example, violations of the FDCA may be a predicate for state-law tort claims.<sup>18</sup> Moreover, competitors, consumer groups, and others often challenge FDA's approvals and clearances.<sup>19</sup> FDA's new theory of "intended use" will provide additional grounds for such challenges. Thus, agency "discretion" is no panacea.

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<sup>18</sup> See, e.g., Talley v. Danek Med., Inc., 179 F.3d 154, 160-61 (4th Cir. 1999); In re Bendectin Litig., 857 F.2d 290, 313 (6th Cir. 1988); Stanton v. Astra Pharm. Prods., Inc., 718 F.2d 553, 563 (3d Cir. 1983). An interesting example presently is awaiting the Supreme Court's decision whether to grant certiorari. See In re Orthopedic Bone Screw Prods. Liability Litig., 159 F.3d 817 (3d Cir. 1998), pet. for cert. filed, 67 U.S.L.W. 3684 (U.S. May 3, 1999) (No. 98-1768). In that case, FDA refused to clear a follow-on device application with labeling claiming an established off-label use, but approved an amended notification that included only the established labeled uses of the predicate device. The Third Circuit held that the manufacturer's omission of a foreseen and desired off-label uses was actionable under a state law tort theory of "fraud on the FDA." Id. at 829.

<sup>19</sup> See, e.g., Serono Labs., Inc. v. Shalala, 158 F.3d 1313, 1316-17 (D.C. Cir. 1998); Schering Corp. v. FDA, 51 F.3d 390, 395 (3d Cir. 1995).

In fact, however, FDA does not require applications for pioneer drugs or devices to justify all foreseeable uses. Nor does it reject ANDA or "substantially equivalent" device applications because the pioneer product has foreseeable and desired off-label uses. It also does not seize articles as misbranded just because they have foreseeable and desired off-label uses even if those are the only economically significant remaining uses for the product. The stark contrast between FDA's assertion in the Pediatric Rule of regulatory authority over foreseeable, unclaimed drug uses and FDA's actual practices – which demonstrate that FDA actually regulates only claimed uses – highlights the arbitrary and capricious nature of FDA's newly adopted regulations comprising the Pediatric Rule.

**E. Despite FDA's Claims To Deference, The FDCA Must Be Given A Harmonious And Consistent Construction That Allows All Of Its Parts To Function As Congress Planned.**

The FDCA is a complex statute with many interacting parts. In construing the similarly complex Internal Revenue Act, this Court said:

The true meaning of a single section of a statute in a setting as complex as that of the revenue acts, however precise its language, cannot be ascertained if it be considered apart from related sections, or if the mind be isolated from the history of the . . . legislation of which it is an integral part.

Commissioner v. Engle, 464 U.S. 206, 223 (1983). Thus, Engle held that the "duty" of a reviewing court is:

to find that interpretation which can most fairly be said to be imbedded in the statute, in the sense of being most harmonious with its scheme and with the general purposes that Congress manifested.

Id. at 215; see also FTC v. Mandel Bros., Inc., 359 U.S. 385, 389 (1959) ("[O]ur task is to fit, if possible, all parts into an harmonious whole."); Gustafson v. Alloyd Co., 513 U.S. 561, 570



(1995) ("The 1933 Act, like every Act of Congress, should not be read as a series of unrelated and isolated provisions.").

To be sure, FDA's statutory interpretations are entitled to deference if the Act is ambiguous. See Chevron U.S.A. Inc. v. National Resources Defense Council, Inc., 467 U.S. 837 (1984). That principle, however, only sets the framework for judicial analysis; it does not displace it. See Engle, 464 U.S. at 216, 225. Thus, an agency's claim to deference cannot permit an agency to inject avoidable disharmony or disregard an "embedded" statutory meaning. See id. at 216, 225 (disapproving an administrative construction even though it could "be reconciled with the language of the statute itself").

An important element of harmony is consistency. The Supreme Court has rejected constructions that require giving inconsistent meanings to the same words in the same statute. See, e.g., National Bank v. Independent Ins. Agents, Inc., 508 U.S. 439, 460 (1993); BankAmerica Corp. v. United States, 462 U.S. 122, 128-29 (1983). It also has avoided new definitions for terms with settled meanings that have been widely understood and relied upon. See id. at 130-32. Where, as here, "the business community directly affected and the enforcing agency [and] the Congress have read [a] statute the same way for 60 years," consistency has a powerful claim. Id.

As previously noted, and despite FDA's contrary assertions, FDA's new theory is contrary to the well-settled understanding by FDA, the courts, and Congress of the "intended use" concept. Important statutory provisions that are understandable and functional when "intended use" is determined by claims would become unworkable under FDA's new theory. Far from seeking harmony and consistency, FDA's new theory is mere expediency, a linguistic juggle intended solely to create jurisdiction over off-label uses that Congress never intended.

V. **FDA'S ABRUPT REVERSAL OF POSITION AS TO ITS AUTHORITY TO REGULATE OFF-LABEL USES CONTRAVENES ITS LONG-STANDING REPRESENTATIONS ON THIS MATTER.**

As previously discussed, for years FDA conceded that its jurisdiction extended to claimed drug uses only. See supra pp. B-12 to B-15. FDA's representations with respect to off-label pediatric uses in particular were no less equivocal. Indeed, former FDA Commissioner David Kessler admitted that FDA lacked authority to require a manufacturer to conduct pediatric studies of a drug for which the manufacturer did not wish to seek approval for pediatric use:

Despite the ardent desire of the FDA to increase pediatric indications, I need to acknowledge the limits of FDA's authority. It is our job to review drug applications for the indications suggested by the manufacturer. We do not have the authority to require manufacturers to seek approval for indications which they have not studied.

Thus, as a matter of law, if an application contains indications only for adults, we're stuck.

...  
The FDA cannot require firms to submit applications. We cannot require companies to conduct trials on products they no longer want to pursue.

... [D]espite [FDA's] public health mandate, the FDA cannot compel firms to conduct trials or pursue promising leads.<sup>20</sup>

In promulgating the Pediatric Rule, FDA has done a complete about-face from Dr. Kessler's remarks on this issue. Despite the admission by FDA's former Commissioner that "FDA cannot compel firms to conduct trials" on pediatric populations of a drug for which the manufacturer seeks approval for adults only, FDA now asserts the authority to require precisely

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<sup>20</sup> David Kessler, Speech of FDA Commissioner to the American Academy of Pediatrics (Oct. 14, 1992); see H.R. Rep. No. 105-310, at 25 (1997) ("FDA has never had freedom to require evidentiary showings that exceed what is required under the law for an approval.").

such testing. See 21 C.F.R. § 314.55(a) (requiring NDA to contain “data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective”); id. § 201.23(a) (warning that manufacturers of marketed drugs whose labels “do[] not provide adequate information to support its safe and effective use in pediatric populations for the approved indications may be required to submit an application containing data adequate to assess whether the drug product is safe and effective in pediatric populations”). FDA’s current view that it can, indeed, force manufacturers to seek approval for off-label uses of their drugs is utterly inconsistent with Dr. Kessler’s concession that FDA lacks “authority to require manufacturers to seek approval for indications which they have not studied.”<sup>21</sup>

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<sup>21</sup> Despite the previously universal consensus that off-label uses include pediatric uses of a drug approved for adult use only, FDA now claims that such pediatric uses do not constitute off-label uses. See 62 Fed. Reg. at 43,907. Specifically, FDA argues that children no longer are “viewed as a population entirely distinct from adults” but rather as a “demographic subpopulation.” Id. at 43,900-01. Therefore, according to FDA, “use of a drug in children is no longer considered a new indication” but is now merely a use of a product for its “approved indications in a significant subpopulation.” Id. at 43,901, 43,907; see 63 Fed. Reg. at 66,634, 66,657.

FDA’s effort to revise what is generally understood is internally inconsistent. On one hand, FDA pretends that children are not a distinct population but merely a “demographic subpopulation with many similarities to the adult population.” See 62 Fed. Reg. at 43,901. On the other hand, FDA has imposed extensive and onerous new testing requirements – and even required manufacturers to develop entirely new formulations of their drug – specifically for that so-called “subpopulation.” See 21 C.F.R. §§ 201.23(a), 314.55(a); see also 62 Fed. Reg. at 43,901 (“Correct pediatric dosing cannot necessarily be extrapolated from adult dosing information . . . . Potentially significant differences in pharmacokinetics may alter a drug’s effect in pediatric patients.”). The stark contrast between FDA’s justification for the Rule based on the professed similarities between adults and children and the dramatically different testing

(Continued . . .)

Given such a dramatic reversal, the Pediatric Rule will come under far more exacting scrutiny should this Citizen Petition culminate in a court challenge. See, e.g., Good Samaritan Hosp. v. Shalala, 508 U.S. 402, 417 (1993) ("An agency interpretation of a relevant provision which conflicts with the agency's earlier interpretation is entitled to considerably less deference than a consistently held agency view." (internal quotations omitted)); Telecommunications Research & Action Center v. FCC, 836 F.2d 1349, 1357 n.19 (D.C. Cir. 1988) ("As we have often said, the weight we accord an agency interpretation is determined in part by the interpretation's consistency with prior agency pronouncements, as well as the length of time the agency has applied its interpretation and whether the agency made its interpretation contemporaneously with the enactment of the statute." (internal quotations omitted)). In light of the Pediatric Rule's irrationality and inconsistency with FDA's interpretation of the FDCA in other contexts, the Pediatric Rule will be unable to withstand such scrutiny.

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(... Continued)

and formulation requirements mandated for that supposedly similar "subpopulation" undercuts FDA's efforts to consider off-label pediatric uses as being within a manufacturer's intended use.

C

US OFFICE PRODUCTS

## APPENDIX C:

### NONE OF FDA'S ASSERTED JUSTIFICATIONS PROVIDE THE NECESSARY STATUTORY AUTHORITY FOR THE PEDIATRIC RULE.

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## APPENDIX C:

### **NONE OF FDA'S ASSERTED JUSTIFICATIONS PROVIDE THE NECESSARY STATUTORY AUTHORITY FOR THE PEDIATRIC RULE.**

In addition to the numerous shortcomings of the Pediatric Rule previously discussed, the statutory authority relied upon by FDA to support the issuance of the Rule is clearly insufficient. "It is axiomatic that an administrative agency's power to promulgate legislative regulations is limited to the authority delegated by Congress." Bowen v. Georgetown Univ. Hosp., 488 U.S. 204, 208 (1988); accord Railway Labor Executives' Ass'n v. National Mediation Bd., 29 F.3d 655, 670 (en banc) ("[I]t is beyond cavil that an agency's power is no greater than that delegated to it by Congress." (internal quotations omitted)), amended by 38 F.3d 1224 (D.C. Cir. 1994); American Fin. Servs. Ass'n v. FTC, 767 F.2d 957, 965 (D.C. Cir. 1985) ("The extent of [an agency's] powers can be decided only by considering the powers Congress specifically granted it in the light of the statutory language and background.").

In apparent recognition of this well-established principle, FDA has invoked a hodgepodge of miscellaneous statutory provisions in support of the Pediatric Rule. None of the relied-upon provisions, however, provide FDA with the requisite statutory authorization to require manufacturers to (1) conduct clinical studies of drug uses for which they do not intend to seek approval and (2) devise formulations of the drug tailored to those uses. Far from being a permissible exercise of delegated authority, FDA's promulgation of the Pediatric Rule represents an unprecedented and unauthorized foray into controlling the marketing decisions of private drug companies concerning which drug uses to pursue and which formulations to develop. FDA should therefore heed the words of its former Commissioner by acknowledging its lack of legal authority to promulgate such regulations and immediately revoke the Rule.

**I. FDA'S AUTHORITY TO PROHIBIT "FALSE OR MISLEADING" LABELING CANNOT SUPPORT THE RULE.**

FDA has asserted that its authority to prohibit "false or misleading" labeling provides the necessary basis for the Pediatric Rule. See 63 Fed. Reg. at 66,657. Specifically, FDA claims that it may find the labeling for a new or marketed drug to be "false" and/or "misleading" if it does not include information supporting the use of that drug on pediatric populations - even though the label explicitly states that the drug is for use by adults only and has not been tested on children. Based on this supposedly "misleading" labeling, FDA can then either deny the NDA if the drug is a new drug or, if the drug is already on the market, declare the product to be "misbranded." See 21 U.S.C. §§ 352(a), 355(d)(7) (1994 & Supp. III 1997). The commonsense definition of "misbranding," however, demonstrates that this argument is fatally flawed, as do FDA's own pre-Pediatric Rule regulations.

As an initial matter, even the term "misbranded" belies FDA's conclusion. By its nature, that term suggests that any alleged "misbranding" can be remedied by changing the wording on the label. FDA's reliance on its "misbranding" authority as giving it broad power to require additional clinical studies and the development of pediatric formulations - as opposed to a reworded disclaimer - is misplaced.

Moreover, FDA's pre-Pediatric Rule regulations already ensure that the labeling for drugs that the manufacturer seeks or has obtained approval to market for adult use only will not be "false" or "misleading" with respect to pediatric uses. Specifically, pre-Pediatric Rule regulations require the label to include detailed information fully disclosing not only information concerning use of the product on adults but also the "limitations of usefulness of the drug" on



pediatric populations. 21 C.F.R. § 201.57; id. § 201.57(c)(3)(i) (1999). In the pediatric context, for example, FDA regulations unambiguously provide that:

If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling shall contain the following statement: "Safety and effectiveness in pediatric patients have not been established."

Id. § 201.57(f)(9)(v). FDA also requires any hazards associated with use of the drug on pediatric populations to be described in the labeling. See id. It is hard to imagine how a label accurately disclosing the lack of testing on children of a drug marketed exclusively for adult use could be considered "false."

Nor can such labeling credibly be deemed "misleading." According to one dictionary, the term "mislead" means "to lead in a wrong direction or into a mistaken action or belief often by deliberate deceit."<sup>1</sup> Labeling that unambiguously discloses that an adult-use drug has not been established to be safe or effective for pediatric populations would not lead any reasonable person to believe incorrectly that it is safe and effective for children. Rather, people accurately conclude that insufficient data exist to support use of the drug on pediatric populations and that FDA therefore has approved the product for adult use only.

With respect to already marketed drugs, Congress has provided additional guidance as to what constitutes misleading labeling for purposes of declaring a marketed drug to be "misbranded." Specifically, Congress has allowed FDA to consider:

not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising

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<sup>1</sup> Merriam-Webster's Collegiate Dictionary 744 (10th ed. 1997); accord The American Heritage Dictionary 803 (2d ed. 1982) (defining "mislead" as "[t]o lead in the wrong direction" or "[t]o lead into error or wrongdoing in action or thought; deceive").

fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

21 U.S.C. § 321(n) (1994).<sup>2</sup> In other words, both affirmative representations and omissions of material facts concerning consequences resulting from both labeled and customary uses of the drug are relevant to the determination of whether a label is "misleading." Even if pediatric use of an adult-use drug might be "customary or usual" in some circumstances, however, a label fully disclosing that an adult-use drug has not been established to be safe or effective in pediatric populations cannot be misleading: The label contains neither affirmative representations nor omissions that would lead a reasonable person to believe erroneously that such safety and effectiveness had been established. On the contrary, the labeling would have to be wholly disregarded for someone to reach this false conclusion.

In sum, FDA cannot rely upon its authority to prohibit misleading labeling to justify the Pediatric Rule. FDA's own pre-Pediatric Rule regulations already ensure that the labels for adult-use drugs contain accurate and complete disclosures concerning (1) use of the drug on adults, and (2) the lack of sufficient information concerning the drug's safety and effectiveness on pediatric patients to support use on that population.

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<sup>2</sup> Congress did not apply this provision to new drugs, perhaps because new drugs have not yet been marketed and therefore cannot have acquired "customary or usual" uses.

## **II. FDA'S AUTHORITY TO BAN DRUGS THAT ARE DANGEROUS WHEN USED IN THE MANNER PRESCRIBED, RECOMMENDED, OR SUGGESTED IN THE LABELING CANNOT SUPPORT THE RULE.**

In a further attempt to justify the Pediatric Rule, FDA has declared drugs approved for use on adults but not on pediatric populations to be "dangerous to health" when used in the manner "prescribed, recommended, or suggested in the labeling thereof." 63 Fed. Reg. at 66,657; 21 U.S.C. §§ 352(j), 355(d) (1994 & Supp. III 1997). Based on the alleged "danger" of such drugs, FDA now asserts the authority to require manufacturers to conduct pediatric studies and develop appropriate pediatric formulations to render the drug "safe" for use. See 21 C.F.R. § 201.23(a) (providing that manufacturer of marketed drug "may be required to submit an application containing data adequate to assess" safety and effectiveness of drug, including dosage and administration in some or all pediatric subpopulations and "may also be required to develop a pediatric formulation"); id. § 314.55(a) (requiring new drug manufacturers to conduct pediatric studies and develop pediatric formulations). If the manufacturer of a new drug does not conduct such studies and develop appropriate pediatric formulations, FDA presumably would refuse to approve the NDA on the ground that the drug has not been shown to be "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." See 21 U.S.C. § 355(d). For marketed drugs, FDA threatens to declare the drug to be misbranded on the ground that it is "dangerous to health when used in the dosage or manner; or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof." See id. § 352(j). FDA's reliance upon the purported "danger" of an adult-use drug, however, is misplaced.

For FDA to invoke § 352(j) or § 355(d), it is not enough for it to assert that a drug is "dangerous" in the abstract. Indeed, even a drug as seemingly innocuous as Tylenol can be

dangerous when used in ways that violate the labeled directions for use. Rather, the drug must be dangerous when used in the manner “prescribed, recommended, or suggested in the labeling thereof” for FDA to ban it on this ground. 21 U.S.C. §§ 352(j), 355(d); accord American Pharm. Ass’n v. Weinberger, 377 F. Supp. 824, 828 (D.D.C. 1974) (“[T]he term ‘safe’ is used in conjunction with the phrase ‘for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.’ When taken in this context, a determination of whether a drug is ‘safe’ is premised on the drug’s use in the ‘prescribed, recommended, or suggested’ manner.”). aff’d sub nom. American Pharm. Ass’n v. Mathews, 530 F.2d 1054, 1055 (D.C. Cir. 1976). Congress’s clear reference to the labeling ensures that FDA may only ban drugs as “dangerous” pursuant to § 352(j) if they are unsafe when used in a manner proposed by the label.<sup>3</sup>

As previously noted, the label for a drug approved for adult use only does not propose use of the product on pediatric populations. See supra pp. C-2 to C-4. Rather the label must contain an express disclaimer advising that “[s]afety and effectiveness in pediatric patients have not been established.” 21 C.F.R. § 201.57(f)(9)(vi). Such a label cannot be considered even to suggest

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<sup>3</sup> Similarly, FDA’s reliance on § 351 of the Public Health Service Act (“PHSA”), which requires biological products introduced into interstate commerce to be “safe, pure, and potent,” to support the Pediatric Rule is misplaced because biologics are subject to the same safety and efficacy requirements as drugs. See 42 U.S.C. § 262 (1994 & Supp. III 1997). Before a manufacturer may submit an application to receive a license for its biologic pursuant to the PHSA, a biologic product must first have been studied under an Investigational New Drug Application. See 21 C.F.R. Part 601; FDA, Center for Biologics Evaluation and Research, Frequently Asked Questions (last modified Sept. 23, 1999) <<http://www.fda.gov/cber/faq.htm>>. Only after “studies demonstrate that the product is safe and effective for its intended use” may a manufacturer submit data to the Center for Biologics Evaluation and Research as part of a biologics application. See id. Once a biologics license has been approved, FDA may revoke the license if it finds that “the licensed product is not safe and effective for all of its intended uses.” 21 C.F.R. § 601.5(b)(6) (1999). In any event, interpreting “safe” under the PHSA more broadly than “safe” under the FDCA would eviscerate the carefully crafted drug approval scheme that Congress established in the FDCA.

much less prescribe or recommend – use of the drug on pediatric populations, and FDA’s contrary claim that an off-label use can be “suggested in a drug’s labeling” even if that “use is not expressly recommended or is even disclaimed,” 63 Fed. Reg. at 66,658, contradicts congressional intent and judicial pronouncements on this phrase. See App. B, pp. B-3 to B-12. This is particularly true for prescription drugs, where no serious claim can be made that a highly trained physician would read an explicit disclaimer instead as a “suggestion” for use. Rather, the fact that “suggested” – like “prescribed” and “recommended” – is modified by the phrase “in the labeling” demonstrates that “suggested in the labeling” refers to an explicit proposal for action in the labeling itself, of the same order as “prescribe” or “recommend,” as in “the physician may wish to consider.”

FDA’s reliance upon 21 U.S.C. § 352(j) with respect to marketed drugs is particularly problematic. To declare a marketed drug misbranded based on this provision, FDA bears the burden of establishing that the drug is dangerous. For the drug to be on the market in the first place, the applicant must necessarily have demonstrated to FDA’s satisfaction that the product is “safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.” See 21 U.S.C. § 355(d). It is arbitrary, to say the least, for FDA now to do a complete about-face and declare that those same products are now unsafe as a general matter. See, e.g., Good Samaritan Hosp. v. Shalala, 508 U.S. 402, 417 (1993) (agency position that conflicts with earlier agency position is entitled to less deference). Moreover, the mere fact that such products have not been tested on pediatric populations does not establish that they are dangerous. It simply establishes that no conclusions can be drawn as to the safety of these products in those populations.

FDA's chosen method of forcing compliance with the Pediatric Rule further demonstrates that FDA has exceeded its authority in promulgating the Rule. If a drug is truly "dangerous to health" as FDA suggests, then the appropriate remedy would be to declare the drug to be misbranded and withdraw it from the market to protect the public. See 21 U.S.C. §§ 334, 355(j) (1994 & Supp. III 1997) (authorizing seizure of misbranded drugs). FDA, however, has declared that it does not intend to remove the offending drugs from the market. Rather it intends to seek court injunctions requiring manufacturers to conduct the testing required by the Pediatric Rule. See 63 Fed. Reg. at 66,655.

An injunction such as the one FDA declares that it will seek would be mandatory rather than prohibitory because it would affirmatively alter manufacturers' legal obligations rather than prohibiting manufacturers from performing a certain task in the future. Mandatory injunctions are disfavored in the courts, and FDA cannot establish its right to this drastic remedy through this rulemaking. As the Tenth Circuit has stated, "[i]t is fundamental that mandatory injunctive relief should be granted only under compelling circumstances inasmuch as it is a harsh remedial process not favored by the courts." Citizens Concerned for Separation of Church & State v. City & County of Denver, 628 F.2d 1289, 1299 (10th Cir. 1980); see also Malkentzos on Behalf of MM v. DeBuono, 102 F.3d 50, 54 (2d Cir. 1996) ("[A] party moving for a mandatory injunction, which alters the status quo by commanding some positive act, must meet a higher standard."). FDA's rejection of the traditional remedies for safeguarding the public health against "dangerous" drugs in favor of a contrived, ad hoc, and judicially disfavored remedy further highlights the legally unsound premises upon which the Pediatric Rule rests.

In sum, FDA lacks the claimed legislative authority to require manufacturers to conduct pediatric studies and develop pediatric formulations for their new or marketed adult-use drugs

based upon an improper characterization of those products as "dangerous" for use under the conditions prescribed, recommended, or suggested in the labeling thereof. Where the manufacturer never sought approval to market the drug for pediatric populations to begin with, and where the labeling for that drug explicitly warns that safety on pediatric populations has not been established, use of the product on pediatric populations is not a use "prescribed, recommended, or suggested" in the product's labeling.

### **III. FDA'S AUTHORITY UNDER 21 U.S.C. § 352(F) TO REQUIRE CERTAIN DRUG LABELS TO "BEAR[] ADEQUATE DIRECTIONS FOR USE" CANNOT SUPPORT THE RULE.**

To justify the Pediatric Rule, FDA also invokes 21 U.S.C. § 352(f), which allows FDA to declare a drug to be misbranded if its label does not bear "adequate directions for use." 63 Fed. Reg. at 66,657-58. Specifically, FDA claims that the labels of drugs approved for adult use do not bear adequate directions for use because they do not contain directions for use of the drug on pediatric populations, which FDA characterizes as a "common" use if an adult-use drug treats a disease affecting both adults and children. See id. at 66,658. FDA further asserts that it may therefore require manufacturers to conduct studies of, and obtain approval for, use of their drug on pediatric populations or forbid the manufacturer from marketing the drug at all by declaring it to be "misbranded." See id. at 66,658; 21 U.S.C. § 352(f). Once again, FDA's purported justification of the Pediatric Rule is fundamentally flawed.

With respect to prescription drugs, "adequate directions for use," according to FDA, exist where:

Labeling on or within the package from which the drug is to be dispensed bears adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for

which it is intended, including all purposes for which it is advertised or represented.

21 C.F.R. § 201.100 (1999). For nonprescription drugs, “adequate directions for use means directions under which the layman can use a drug safely and for the purposes for which it is intended.” *Id.* § 201.5. Despite FDA’s claim that “intended uses” include both claimed and foreseeable uses and that adequate directions for both must appear on a product’s labeling, *see id.* § 201.128 (1999), the “intended uses” of a drug encompass only those claimed by the manufacturer, *see* App. B, pp. B-3 to B-15. Indeed, major portions of food and drug law would become inoperable and unintelligible if “intended uses” of a product encompassed foreseeable uses in addition to labeled uses. *See* App. B, pp. B-15 to B-22. FDA cannot, under the guise of ensuring that products bear “adequate directions for use,” expand its authority to require manufacturers to bring on-label any and all foreseeable off-label uses.<sup>4</sup>

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<sup>4</sup> FDA’s reliance on its 1952 regulation defining the words “intended uses” is misplaced. *See* 63 Fed. Reg. at 66,657-58. *Compare* 21 C.F.R. § 201.128 *with* 21 C.F.R. § 1.106(o) (1952) (demonstrating identity of “intended use” portions of current regulations to version promulgated in 1952). Even if the regulation could somehow be read to support FDA’s novel foreseeability theory, for years following the 1952 issuance of the regulation, FDA repeatedly represented that its regulatory authority extended only to claimed uses of a product. *See* App. B, pp. B-12 to B-15. In any event, an agency regulation cannot override congressional intent as evidenced in the governing statutes. As the Supreme Court has long held, “[t]he rulemaking power granted to an administrative agency charged with the administration of a federal statute is not the power to make law. Rather, it is the power to adopt regulations to carry into effect the will of Congress as expressed by the statute.” *Ernst & Ernst v. Hochfelder*, 425 U.S. 185, 213 (1976) (internal quotations omitted). Indeed, the considerable reluctance with which Congress gave FDA even extremely narrow authority to consider uses of a device not identified in the product’s labeling in connection with FDAMA confirms that Congress has always intended that FDA’s regulatory authority be limited to claimed uses of a product, absent an explicit congressional authorization to the contrary. *See* App. B, pp. B-8 to B-9.



In sum, FDA's jurisdiction to regulate drugs extends only so far as the uses for which the manufacturer seeks approval. It does not include the right to require manufacturers to seek approval for pediatric populations of a drug labeled for adult use only. Rather, use on children of a drug approved for adult use only is exclusively within the province of (1) the manufacturer, by deciding to seek approval for pediatric populations and (2) the medical profession, which may exercise professional judgment in prescribing the product off-label for pediatric populations.

#### **IV. FDA'S AUTHORITY TO REQUIRE SUBMISSION OF DATA CONCERNING INVESTIGATIONAL USE AND TESTING OF DRUGS CANNOT SUPPORT THE RULE.**

In a further attempt to justify the pediatric studies requirement embodied in the Pediatric Rule, FDA relies upon its ability to require manufacturers to submit reports of the data obtained as a result of the investigational use and/or clinical testing of a drug. See 21 U.S.C. § 355(i) (authorizing FDA to require submission of data "obtained as the result of [the] investigational use of [a] drug" as a precondition for allowing such use); id. § 355(k) (1994) (authorizing FDA to require submission of "data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug" to enable FDA to determine whether grounds exist for withdrawal of approval of drug). These provisions, however, only contain reporting requirements concerning clinical studies and other available information with respect to the drug at issue; they do not authorize FDA to require the manufacturer to generate new data – i.e., by conducting additional clinical studies – particularly for indications for which the manufacturer does not seek approval.<sup>5</sup>

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<sup>5</sup> Tellingly, the Conference Report accompanying FDAMA characterizes § 355(i) concerning requirements for clinical investigations of a drug as "[s]reamlining clinical research on drugs." H.R. Conf. Rep. No. 105-399, at 21.

Moreover, had Congress intended to grant FDA the authority to require the submission of additional studies beyond those necessary to support use of the drug for its labeled indications, it knew how to do so. Cf. Railway Labor Executives' Ass'n, 29 F.3d at 666 ("[W]here Congress meant . . . to authorize the Board to offer its services, it did so explicitly."). In the recently enacted FDAMA, for example, Congress explicitly authorized FDA to impose post-approval study requirements for drugs approved pursuant to the fast-track procedures. 21 U.S.C. § 356(b)(2) (1994 & Supp. III 1997); see also H.R. Rep. No. 105-310, at 56 (observing that FDAMA provision "provides the Secretary with the authority to impose such [post-approval study] requirements but does not require this"). There is no similar provision, by contrast, authorizing FDA to impose additional studies beyond those required to support usage of the drug for indications referred to on the label. FDA simply cannot craft out of whole cloth a requirement that manufacturers conduct research for off-label indications based on statutes merely designed to keep FDA informed of preexisting data concerning the drug.

**V. FDA CANNOT RELY UPON ITS AUTHORITY "TO ISSUE REGULATIONS FOR THE EFFICIENT ENFORCEMENT OF THE ACT" TO JUSTIFY THE RULE ABSENT AN INDEPENDENT GRANT OF STATUTORY AUTHORITY.**

FDA also relies upon its authority "to issue regulations for the efficient enforcement of the Act" pursuant to 21 U.S.C. § 371. This provision, however, does not give FDA carte blanche to promulgate regulations beyond what Congress has authorized. Rather, it simply provides that FDA may issue regulations to implement Congress's intent as expressed elsewhere in the FDCA. Absent an independent statutory basis for the Pediatric Rule, this provision grants no authority to FDA to issue the Rule.

It is well-settled that although FDA may reasonably interpret FDCA provisions, it does not have "the power to make law. Rather, it [has] the power to adopt regulations to carry into effect the will of Congress as expressed by the statute." Hochfelder, 425 U.S. at 213-14 (citation and internal quotations omitted). Under the standard for judicial review of agency statutory interpretations, FDA is entitled to "deference," but only if the FDCA is unclear or ambiguous. Chevron U.S.A. Inc. v. National Resources Defense Council, Inc., 467 U.S. 837, 842-43 (1984). Moreover, even if the FDCA is unclear, FDA's interpretation must be reasonable. Id. In light of the conflicting Pediatric Exclusivity provisions in FDAMA and the complete lack of statutory authority for FDA to promulgate the Pediatric Rule, a court could only conclude that FDA had acted unreasonably and invalidate the Rule.

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## US OFFICE PRODUCTS

## APPENDIX D:

### **THE PEDIATRIC RULE IS CONSTITUTIONALLY DEFICIENT BECAUSE IT PURPORTS TO AUTHORIZE "TAKINGS" OF PRIVATE PROPERTY FOR PUBLIC USE WITHOUT JUST COMPENSATION.**

A key purpose of the Takings Clause of the Fifth Amendment to the United States Constitution is "to bar Government from forcing some people alone to bear public burdens which, in all fairness, should be borne by the public as a whole." Armstrong v. United States, 364 U.S. 40, 49 (1960). Yet that is precisely what the Pediatric Rule seeks to do – impose on pharmaceutical manufacturers the burden of discovering new uses for certain chemical compounds even if they have no desire to market those drugs for those uses. The taking is particularly obvious with respect to drugs that are already on the market. With respect to such drugs, FDA is asserting the authority to command manufacturers to reformulate the drug and spend what could be massive amounts of research funds to assess whether the drug is safe and effective in pediatric populations. What is more, FDA claims this power even if the manufacturer has disclaimed any pediatric use. This is hardly different from the government commanding one private citizen, as a condition of driving to work on a particular road, to erect warning signs on that road for all to see.

The taking is no less egregious with respect to drugs that are not yet on the market. FDA approval is not the conferral of a public benefit. It is an approval that one must secure before using one's own property. FDA may not condition its approval of that property right on the dedication to the public of potentially massive resources in the form of research into the potentially foreseeable pediatric uses of the product. The government can no more impose such a condition on its approval than a land-use commission can condition an approval to build a new

factory on the builder's simultaneous financing of a local school. See Nollan v. California Coastal Comm'n, 483 U.S. 825, 837 (1987) (characterizing an attempt to achieve a public easement as a condition of approving a land use as "an out-and-out plan of extortion" (internal quotations and citation omitted)).

Here, as in Dolan v. City of Tigard, 512 U.S. 374, 388 (1994), "the degree of the exactions" demanded by FDA's conditions do not bear the "required relationship to the projected impact" of the manufacturer's proposal to sell these drugs. The government may not require manufacturers to undertake massive research for the public's benefit or use when they themselves do not intend to benefit by such use, and when they manifest that intention by not claiming such a use. Essentially, the government is using the drug manufacturer's marketing of the drug or request for approval of a new drug "as an excuse for taking property simply because at that particular moment" the government is being asked for an approval. Id. at 390. Put simply, FDA may not require the manufacturers to dedicate private property – i.e., their research funds and facilities – for some future public use as a condition either of continuing to market the drug or of obtaining approval to market the drug for a different purpose.<sup>1</sup>

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<sup>1</sup> The Supreme Court has made clear that "simply denominating a government measure as a 'business regulation' does not immunize it from constitutional challenge on the ground that it violates a provision of the Bill of Rights." Dolan, 512 U.S. at 392.

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US OFFICE PRODUCTS

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IN THE UNITED STATES COURT OF APPEALS  
FOR THE DISTRICT OF COLUMBIA CIRCUIT

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WASHINGTON LEGAL FOUNDATION,

Plaintiff-Appellee,

v.

JANE E. HENNEY, in her official capacity as  
Commissioner, Food and Drug Administration,  
and DONNA SHALALA, in her official capacity as  
Secretary, Department of Health and Human Services,

Defendants-Appellants.

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ON APPEAL FROM THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF COLUMBIA

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**III. The Food And Drug Administration Modernization Act Of 1997 Is Fully Consistent With The First Amendment.**

Even if WLF has standing to sue, the district court erred in invalidating the FDAMA. The FDAMA is concerned exclusively with commercial speech. The statute regulates the dissemination of information that promotes an unlawful commercial transaction: the introduction into interstate commerce of drugs and medical devices for intended uses that the FDA has not approved as safe and effective. The FDAMA does not restrict the dissemination of information outside the context of such an illegal commercial transaction. Academics, scientists, and members of the public at large are free to disseminate any information about off-label uses that they desire. Indeed, even manufacturers are free to disseminate off-label information in response to a request by a physician. It is only when manufacturers use such dissemination to promote the illegal dissemination of a drug or device that FDAMA applies. See 21 U.S.C. § 360aaa-6(a).

Thus, the district court correctly held that the FDAMA must be evaluated under the test that governs the regulation of commercial speech. Under that analysis, commercial speech "related to illegal activity" is not entitled to First Amendment protection. Central Hudson Gas & Electric Corp. v. Public Service Comm'n of New York, 447 U.S. 557, 563-64 (1980). Commercial speech that "concern[s] lawful activity and [is] not \* \* \* misleading" may be restricted if

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(...continued)  
dissemination is targeted at the individual physicians whom WLF purports to represent.



the government's interest is substantial, the regulation directly advances that interest, and the regulation is no more extensive than necessary to serve that interest. *Id.* at 566.

As explained below, the FDAMA satisfies every element of the Central Hudson analysis. The statute regulates commercial speech related to conduct that has long been illegal under the FDCA and therefore satisfies the first part of the Central Hudson test. As a result, the speech is not protected by the First Amendment. And even if the speech at issue were entitled to First Amendment protection, the FDAMA directly and materially advances substantial governmental interests and does not burden more speech than necessary to further those objectives.

**A. The FDAMA Concerns Illegal Conduct That Is Not Protected By The First Amendment.**

The district court's invalidation of the FDAMA calls into question the most fundamental and longstanding premises of the statutory scheme governing drugs and medical devices. Beginning with the very first federal statute regulating drugs in 1906, the determination of whether a particular product is a "drug" has turned not only on its physical and chemical characteristics, but on the purposes for which the manufacturer intends the product to be used. See 21 U.S.C. § 321(g)(1)(B) (defines the term drug as, *inter alia*, an article "intended for use" in the treatment of disease); Action on Smoking and Health v. Harris, 655 F.2d 236, 238 (D.C. Cir. 1980).

Since 1962, Congress has required manufacturers to demonstrate that their new drugs are not only safe, but also "effective" for

each of their intended uses. See 21 U.S.C. § 321(p)(1); Weinberger v. Hynson, Westcott and Dunning, Inc., 412 U.S. 609, 613 (1973). If a new drug is not approved by the FDA as safe and effective for a particular intended use, the manufacturer generally cannot introduce the drug into interstate commerce with the intent that it be used for that purpose. See 21 U.S.C. §§ 331(d), 355. The same holds true with respect to medical devices. See 21 U.S.C. §§ 331(a), 351(f).

Thus, the intended use of a product has always been of central importance in determining whether the product falls under FDA's jurisdiction and whether new intended uses of the product trigger additional approval requirements. The courts have long recognized that manufacturers' claims about the product (either implicit or explicit) are compelling evidence of that intent.<sup>3</sup> And "it is well established 'that the "intended use" of a product, within the meaning of the [FDCA], is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source.'" Action on Smoking and Health, 655 F.2d at 239; see also 21 C.F.R. §§ 201.128, 801.4.

The FDAMA addresses one source of evidence of a manufacturer's intent concerning the uses of its products: the manufacturer's

See, e.g., Action on Smoking and Health, 655 F.2d at 238-39; United States v. Storage Spaces Designated Nos. "8" and "49", 777 F.2d 1363, 1366 (9th Cir. 1985), cert. denied, 479 U.S. 1086 (1987); United States v. An Article of Device . . . Toftness Radiation Detector, 731 F.2d 1253, 1256-57 (7th Cir.), cert. denied, 469 U.S. 882 (1984); United States v. An Article . . . Consisting of 216 Bottles, More or Less . . . Sudden Change, 409 F.2d 734, 739 (2d Cir. 1969); United States v. Article of Drug Designated B-Complex Cholinos, 362 F.2d 923, 925-26 (3d Cir. 1966).



unsolicited dissemination of articles or reference texts discussing off-label uses of its drugs or devices. The unsolicited dissemination of such information is highly persuasive evidence that the manufacturer intends that the product be used in the unapproved manner. And if the manufacturer has not demonstrated that the intended use of the product is safe and effective, the manufacturer's continued introduction of the product into interstate commerce is unlawful as long as the manufacturer continues to intend such use.

As the district court explained, economic actors such as automobile manufacturers and restaurant owners often seek to promote sales to consumers by disseminating or displaying literature about their products prepared by independent organizations. J.A. 746 (13 F. Supp. 2d 51, 63 (D.D.C. 1998)). That is particularly true of drug and medical device manufacturers. As the district court recognized, "[t]he peculiarities of the prescription drug industry make dissemination of scientific research results an especially important and prevalent marketing tool," *ibid.*, because the sale of prescription drugs requires a manufacturer to persuade a physician -- as opposed to a lay consumer -- that the drug will serve its intended purpose. J.A. 746-47 (13 F. Supp. 2d at 63). Thus, the district court recognized that a manufacturer's promotion of a drug or device through the dissemination of scientific literature is a crucial factor that evidences the intended use of a product.

Prior to the enactment of the FDAMA, a manufacturer's dissemination of such information would have been highly relevant and material evidence of a violation of the FDCA's prohibition against the introduction into interstate commerce of drugs and devices for uses the FDA has not approved as safe and effective. The use of a manufacturer's dissemination of information about the off-label uses of its products as evidence of unlawful intent is fully consistent with the First Amendment. As the Supreme Court has explained, "[t]he First Amendment \* \* \* does not prohibit the evidentiary use of speech \* \* \* to prove motive or intent." Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993). Thus, the speech of a manufacturer properly has been used to demonstrate the manufacturer's intent under the FDCA. See United States v. Article of Drug Designated B-Complex Cholinus Capsules, 362 F.2d at 925-27 (manufacturer's intended use of drug determined on the basis of claims made in radio broadcast and in manufacturer's promotional material);.

Moreover, the treatment of the dissemination of off-label information as a separate violation of the FDCA's "misbranding" provision is manifestly consistent with the First Amendment. That provision makes it unlawful for drug and device labeling to omit "adequate directions for use" of the drug. 21 U.S.C. § 352(f). A new drug or device that is distributed for an off-label use is misbranded because the labeling of such a drug or device would not include "adequate directions for use." The product's labeling

could not contain adequate directions for a use that the FDA has not reviewed and approved.

The misbranding prohibition presents no First Amendment problem because the underlying transaction to which the claim relates -- the distribution of an unapproved drug or medical device -- is itself unlawful. The Supreme Court has made clear that speech concerning unlawful activity receives no First Amendment protection. See 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 497 n.7 (1996) (plurality opinion) ("the First Amendment does not protect commercial speech about unlawful activities"); Florida Bar v. Went For It, Inc., 515 U.S. 618, 623-24 (1995) ("the government may freely regulate commercial speech that concerns unlawful activity"); Zauderer v. Office of Disciplinary Counsel of Supreme Court of Ohio, 471 U.S. 626, 638 (1985) ("the States and the Federal Government are free to prevent the dissemination of commercial speech \* \* \* that proposes an illegal transaction"; Bolger v. Youngs Drug Products Corp., 463 U.S. 60, 69 (1983) ("the State may also prohibit commercial speech related to illegal behavior"); Central Hudson, 447 U.S. at 563-64 (1980) ("the government may ban \* \* \* commercial speech related to illegal activity").

The Supreme Court's decision in Pittsburgh Press Co. v. Pittsburgh Comm'n on Human Relations, 413 U.S. 376 (1973), is particularly instructive. That case concerned a municipal ordinance that prohibited a newspaper from carrying a gender-based advertising column for certain positions of employment. The

ordinance also prohibited employers from engaging in gender discrimination with respect to those positions and from publishing, or causing to be published, any advertisement that indicated gender discrimination. Id. at 378, 388-89. The Court recognized that the advertisements at issue "signaled that the advertisers were likely to show an illegal sex preference in their hiring decision." Id. at 389. The Court held that any First Amendment interest in advertising a commercial transaction is "altogether absent when the commercial activity itself is illegal and the restriction on advertising is incidental to a valid limitation on economic activity." Ibid.; see also Central Hudson, 447 U.S. 557, 563-64 (1980).

The same analysis governs this case. Both Pittsburgh Press and this case involve unlawful conduct: Pittsburgh Press involved unlawful gender discrimination, and this case involves the unlawful distribution of drugs and medical devices. In both cases, the commercial speech at issue (the advertisements in Pittsburgh Press and the dissemination of journal articles and textbooks in this case) provides persuasive evidence of the intent or motive that is an element of the unlawful conduct. And here, as in Pittsburgh Press, "the restriction on advertising is incidental to a valid limitation on economic activity." Ibid.

In short, there can be no question that the FDCA's longstanding use of manufacturers' speech to determine the "intended" uses of their products is consistent with the Constitution. Because that traditional feature of the FDCA passes

constitutional muster, the FDAMA also withstands scrutiny.

Indeed, the FDAMA simply establishes a safe harbor for manufacturers, permitting more speech and conduct than would be allowed under the FDCA alone. The FDAMA ensures that manufacturers can disseminate certain journal articles and reference texts discussing off-label uses of their products without violating the FDCA's restrictions on the interstate distribution of drugs and devices. Most important, if a manufacturer complies with the FDAMA, the government cannot use a manufacturer's dissemination of an article or reference text "as evidence of a new intended use of the drug or device that is different from the intended use of the drug or device set forth in the official labeling" of the product. 21 U.S.C. § 360aaa-6(b). Moreover, "[s]uch dissemination shall not be considered by the Secretary as labeling, adulteration, or misbranding of the drug or device." Ibid.

In invalidating the FDAMA, the district court reaffirmed its prior ruling which emphasized that the FDA has not prevented physicians from prescribing drugs for off-label uses. J.A. 802; see J.A. 754-56 (13 F. Supp. 2d at 66). That emphasis is misplaced. Congress has prohibited manufacturers from distributing drugs and devices for off-label uses, and the restrictions retained in the FDAMA similarly apply to actions by manufacturers, not physicians treating patients. The FDAMA prevents the government from using certain scientific information disseminated by manufacturers as evidence of illegal distribution of their drugs and devices. Both the FDCA and the FDAMA ensure that physicians



will not receive biased or incomplete information about the off-label uses of drugs and devices, placing physicians in a better position to make informed judgments about whether to prescribe such products for their patients.

Significantly, the district court did not question Congress's power to ban manufacturers from issuing advertisements or engaging in other forms of commercial speech that overtly promote the off-label uses of their drugs or devices. Yet Congress's decision to regulate the distribution of journal articles and textbooks discussing off-label uses serves precisely the same purpose as its limitation on overt advertising; both forms of regulation are aimed at limiting a manufacturer's promotion of an illegal commercial transaction. If Congress's prohibition of overt advertising satisfies the First Amendment, then the First Amendment also permits Congress to regulate the more subtle but also very effective promotional efforts that occur when a manufacturer affirmatively disseminates favorable scientific information concerning off-label uses. Similarly, although the district court expressly excluded completely unapproved drugs and devices from its order, nothing in the court's decision explains why, under its First Amendment analysis, a manufacturer would not be entitled to promote those products as well.

The district court's decision thus threatens to undermine a longstanding cornerstone of the FDCA. It is Congress's considered judgment that public health is best served by having manufacturers demonstrate to the FDA that their drugs and devices are safe and

effective before those products are distributed for particular intended uses. See United States v. Rutherford, 422 U.S. 544, 551-52 (1979). The court's decision, however, permits manufacturers, in effect, to propose an unlawful transaction -- the sale of their products in interstate commerce for intended uses that have not been proven safe and effective -- without having to scientifically substantiate such uses. To the extent that such promotional efforts are successful, they can be expected to substantially increase the incidence of off-label use. See J.A. 644-45 (noting studies demonstrating direct relationship between manufacturer sponsorship of promotional activities and physician use of manufacturer's products).

The district court's decision thus significantly reduces the incentives of manufacturers to conduct the studies necessary to demonstrate that their products are safe and effective with respect to the uses for which the manufacturer distributes them. If manufacturers can successfully promote off-label uses by selectively disseminating favorable journal articles, there will be less reason to spend the time and money to seek FDA approval for the interstate distribution of the product for those uses. As a result, physicians will actually have less information about the safety and effectiveness of medical products that they prescribe for their patients.

The district court's order places great emphasis on whether an article appears in a "peer-reviewed" professional journal. As the record demonstrates, however, "[r]eliance on peer review is not

an adequate substitute for FDA review, because the peer reviewer has access to only a limited amount of data." J.A. 593; see also J.A. 646, 652. Indeed, "[i]t is difficult, if not impossible to critically evaluate the adequacy of a clinical trial without access to critical raw data and the study protocol." J.A. 593; see also J.A. 652. And "[m]ost practicing physicians and physicians performing peer review for journals have no access to such data." J.A. 593; see also J.A. 652.

Moreover, the district court's order allows the dissemination of an article that is not false or misleading as long as it appears in a "bona fide peer-reviewed professional journal." J.A. 814. However, all parts of such peer-reviewed journals are not necessarily subjected to peer review. See J.A. 646. Unlike the district court's order, the FDAMA specifically requires that the article to be disseminated itself be peer-reviewed, and the article must pertain to a clinical investigation and be scientifically sound. See 21 U.S.C. § 360aaa-1(a)(1)(A); 21 C.F.R. § 99.101(a)(2).

The FDAMA also includes other requirements, in addition to peer review, that ensure the reliability of the disseminated journal article. For example, under FDAMA, the journal must (1) be published by an organization with an editorial board; (2) be generally recognized to be of national scope and reputation; and (3) be indexed in the Index Medicus of the National Library of Medicine of the National Institutes of Health; and (4) not take the form of a special supplement funded in whole or in part by the



manufacturer. 21 U.S.C. § 360aaa-5(5). The district court's order includes no similar protections.

In addition, although the district court limited its ruling to drugs and devices that have been approved by the FDA as safe and effective for at least one use, allowing manufacturers to promote the unapproved uses of those products can pose the same health risks as the promotion of a wholly unapproved drug or medical device. See J.A. 594-95; J.A. 523-24, 526-36. Thus, a drug that a manufacturer may lawfully distribute for treatment of high blood pressure might be equally ineffective in treating cancer as another drug that has not been approved for distribution for any use. The danger to public health in allowing the promotion of either drug for the treatment of cancer would be substantial.

In sum, Congress has long prohibited manufacturers from introducing into interstate commerce drugs and medical devices for uses that the FDA has not approved as safe and effective. Although the promotion of such unlawful activity was previously barred under the FDCA, Congress now permits it to a limited extent under the FDAMA, in the interests of facilitating the disclosure of unbiased scientific information to physicians and encouraging manufacturers to file applications for new uses of their products. Far from being an invalid restriction on speech, the FDAMA expands the range of speech that is permitted under federal law in order to achieve important public health policy objectives.

The district court suggested that the statutory scheme at issue here is analogous to a law "criminalizing criticism of the

government." J.A. 802. That analogy is inapt. This case involves commercial speech and its regulation in connection with conduct that Congress has properly made illegal for over sixty years -- the introduction of products into interstate commerce for uses that have not been proven safe and effective. The FDAMA accordingly raises no First Amendment concerns.

**B. The FDAMA Directly And Materially Advances Substantial Government Interests.**

1. Even if the FDAMA concerned speech that was protected by the First Amendment, the statute is supported by "substantial" government interests, as required under the second part of the Central Hudson analysis. The FDAMA furthers the government's "substantial interest in 'promoting the health, safety, and welfare of its citizens.'" Pearson v. Shalala, 164 F.3d 650, 656 (D.C. Cir. 1999) (quoting Rubin v. Coors Brewing Co., 514 U.S. 476, 485 (1995)). The statute ensures that manufacturers cannot mislead physicians by promoting off-label uses through a biased and selective presentation of favorable materials. Instead, the FDAMA ensures that physicians, managing risks for their patients, receive a balanced package of material that presents a complete and scientifically valid view of the risks and benefits of the off-label use.

Off-label uses of drugs and devices in certain areas (such as pediatrics and oncology) are not uncommon and in some circumstances have made a valuable contribution to patient care. See J.A. 726-27 (13 F. Supp. at 56). Nonetheless, the risk to the public from unproven uses of drugs and devices is both real and substantial.

is not exhaustive. J.A. 486, 503 (62 Fed. Reg. at 64,082, 64,099). Thus, "[t]he supporting company and the provider are free to adopt alternative approaches to help ensure that activities are independent and nonpromotional." J.A. 486 (62 Fed. Reg. at 64,082). Far from banning speech, the Document merely provides a safe harbor from regulation, and, as such, does not run afoul of the First Amendment.

#### CONCLUSION

For the foregoing reasons, the judgment of the district court should be reversed.

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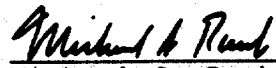
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Michael S. Raab



[SCHEDULED FOR ORAL ARGUMENT ON JANUARY 10, 2000]

No. 99-5304

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IN THE UNITED STATES COURT OF APPEALS  
FOR THE DISTRICT OF COLUMBIA CIRCUIT

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WASHINGTON LEGAL FOUNDATION,

Plaintiff-Appellee,

v.

JANE E. HENNEY, in her official capacity as  
Commissioner, Food and Drug Administration,  
and DONNA SHALALA, in her official capacity as  
Secretary, Department of Health and Human Services,

Defendants-Appellants.

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ON APPEAL FROM THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF COLUMBIA

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## GLOSSARY

ACLU	American Civil Liberties Union
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act of 1997
FDCA	Federal Food, Drug, and Cosmetic Act of 1938, as amended
J.A.	Joint Appendix
PhRMA	Pharmaceutical Research and Manufacturers of America
WLF	Washington Legal Foundation

IN THE UNITED STATES COURT OF APPEALS  
FOR THE DISTRICT OF COLUMBIA CIRCUIT

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No. 99-5304

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WASHINGTON LEGAL FOUNDATION,

Plaintiff-Appellee,

v.

JANE E. HENNEY, in her official capacity as  
Commissioner, Food and Drug Administration,  
and DONNA SHALALA, in her official capacity as  
Secretary, Department of Health and Human Services,

Defendants-Appellees.

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ON APPEAL FROM THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF COLUMBIA

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REPLY BRIEF FOR THE APPELLANTS

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**INTRODUCTION AND SUMMARY OF ARGUMENT**

Washington Legal Foundation ("WLF") and its amici seek to divert the Court's attention from what is actually at issue in this appeal. They devote much of their briefs to arguing that the conduct of physicians in prescribing drugs and medical devices for off-label uses is common, important, and legal. See WLF Br. 3-10, 18, 22-23; PhRMA Br. 3-11. Although we dispute many of their underlying factual assertions, since at least 1972, the Food and Drug Administration ("FDA") has taken the position that physicians may prescribe otherwise approved drugs for unapproved uses provided that they do not promote the drug for such uses. See Opening Br. 8. Thus, the conduct and speech of physicians are not at issue in this case.

Instead, this case concerns the conduct of drug and device manufacturers. Congress has long required manufacturers to obtain FDA approval or clearance for every use for which a new drug or device is promoted. Prior to 1997, the Federal Food, Drug, and Cosmetic Act ("FDCA") absolutely prohibited manufacturers from promoting the unapproved uses of their approved drugs and devices. See pp. 6, 7-9, *infra*.

Section 401 of the Food and Drug Administration Modernization Act of 1997 ("FDAMA") relaxes the restrictions of prior law. In exchange for allowing manufacturers to promote the off-label uses of their products through the dissemination of journal articles and reference texts, Congress generally required manufacturers to agree to perform the scientific studies necessary to demonstrate that the off-label uses are safe and effective and to submit those studies to the FDA for evaluation. See 21 U.S.C. §§ 360aaa(b)(5), 360aaa-3. Congress also directed manufacturers to comply with certain other reasonable requirements to ensure that physicians receive all relevant information about the off-label uses of a manufacturer's products rather than a selective view of the available evidence. As the district court recognized (J.A. 752-53 (13 F. Supp. 2d at 65)), manufacturers have a strong economic incentive to make selective disclosures to physicians, who can increase the sales of drugs and medical devices by prescribing those products for off-label uses.

Thus, the FDAMA promotes the public health by encouraging manufacturers to conduct the studies necessary to demonstrate that

the off-label uses of their products are safe and effective and by ensuring that physicians, managing risks for their patients, receive an unbiased package of material that presents a complete and scientifically accurate view of the risks and benefits of the off-label uses. Moreover, if the studies are conducted and safe and effective new uses are placed on the product's label, then all physicians, and not just those to whom manufacturers selectively distribute information, will have the new uses readily available to them for their patient care. In furthering these objectives, the FDAMA is entirely consistent with the First Amendment.

WLF and its amici argue that the FDAMA is paternalistic. But the statute is not intended to keep physicians ignorant of information about off-label uses. To the contrary, the FDAMA does not regulate the exchange of off-label information among scientists and physicians. Nor does the statute prohibit manufacturers from disclosing off-label information in response to a physician's unsolicited request. See 21 U.S.C. § 360aaa-6(a). The FDAMA addresses unsolicited disclosures by manufacturers with respect to their products, ensuring that physicians do not receive biased or selective information about off-label uses that could distort their treatment decisions.

Moreover, the requirement that drugs and medical devices receive approval from the FDA for each of their intended uses is a longstanding, central, and eminently sensible feature of our food and drug laws. Congress long ago recognized that the FDA is uniquely positioned to weigh the massive volume of complex

scientific data involved before allowing drug and device manufacturers to promote and distribute their products for particular uses. The FDAMA ensures that manufacturers do not circumvent the approval process, and it permits more manufacturer speech than the prior statutory scheme allowed.<sup>1</sup>

#### ARGUMENT

1.a. WLF provides no meaningful response to our central point in this appeal: the FDAMA is focused exclusively on the promotion by manufacturers of the illegal commercial distribution of drugs and devices for uses that the FDA has not approved as safe and effective. Instead, WLF focuses most of its attention on the fact that physicians prescribe drugs and devices for off-label uses.

As explained in our opening brief (at 33-34), the Supreme Court's analysis in Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993), and Pittsburgh Press Co. v. Pittsburgh Comm'n on Human Relations, 413 U.S. 376, 388-89 (1973), governs this case. This case, like Mitchell and Pittsburgh Press, involves unlawful conduct

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<sup>1</sup>In our opening brief (at 26-27), we argued that WLF's generalized interest in protecting private individuals and businesses from "undue interference" by the government (J.A. 13) should not be sufficient to allow the organization to represent the professional interests of the (presumably) relatively small proportion of WLF's members who happen to be physicians, particularly if WLF's "members" are merely financial contributors who exercise no meaningful control over WLF's organization and structure. In response, WLF nowhere explains what it means to be a "member" of WLF. If WLF's physician "members" are simply financial contributors, with no control over the manner in which WLF is governed, then WLF should not be permitted to represent their interests in this suit. See Hunt v. Washington State Apple Advertising Comm'n, 432 U.S. 333, 344 (1977) ("indicia of membership" includes power to elect association's governing body as well as to finance association's activities).

apart from speech: Mitchell involved crimes motivated by bias; Pittsburgh Press involved unlawful gender discrimination in hiring; and this case involves the unlawful distribution of drugs and devices for intended off-label uses. In each case, the speech at issue (discriminatory statements in Mitchell, advertisements in Pittsburgh Press, and the dissemination of certain journal articles and textbooks in this case) provides highly relevant evidence of the intent or motive that is a key element of the unlawful conduct. Moreover, in this case, as in Pittsburgh Press, the direct restrictions on commercial speech are "incidental to a valid limitation on economic activity." Pittsburgh Press, 413 U.S. at 389; see also Opening Br. 33 (collecting cases).

Contrary to the thrust of WLF's brief, the fact that physicians have been able to prescribe drugs and devices for off-label uses does not legalize the manufacturers' distribution of their drugs and devices for such unapproved uses. And the First Amendment affords no protection to the promotion of such illegal distribution. In Pittsburgh Press, the Court held that an advertisement could be prohibited where it "signaled" that the advertiser was "likely" to have an impermissible discriminatory intent. 413 U.S. at 389. There was no suggestion in that case that the job applicants themselves were engaging in unlawful conduct. Thus, a male employee hired pursuant to the discriminatory policy at issue in Pittsburgh Press presumably would have been free to continue working at his job, even though his employer was prohibited from engaging in advertising that "signaled" that the



employer was "likely" to have an impermissible intent in the hiring process.

Contrary to WLF's suggestion (WLF Br. 20), the fact that the FDAMA prohibits the dissemination of information in violation of the statute, 21 U.S.C. § 331(z), poses no First Amendment difficulties. Section 331(z) does not, in effect, subject any manufacturer conduct to regulatory consequences that the FDCA did not already impose. Prior to the enactment of the FDAMA, the unsolicited dissemination to physicians of journal articles and reference texts discussing off-label uses would have been evidence that the manufacturer was distributing its products with the intent that they be used in a manner that the manufacturer had not proven to be safe and effective. The manufacturer's continued interstate distribution of those products would have been unlawful. See 21 U.S.C. §§ 331(a), (d), 351(f), 352(f), 355, 360c(f)(1).

Moreover, a drug or device is "misbranded" if its labeling does not bear "adequate directions for use." 21 U.S.C. § 352(f)(1). Thus, the labeling of a drug or device must indicate all intended uses, including those intended uses that the manufacturer has manifested through its promotional activities. If the labeling does not indicate all intended uses, the product is misbranded, and its interstate distribution is unlawful. See 21 U.S.C. §§ 331(a), 352(f)(1).

b. Amicus Pharmaceutical Research and Manufacturers of America ("PhRMA") attempts to distinguish both Pittsburgh Press and Mitchell on the ground that in those cases "the speech is

distinguishable from the underlying illegal conduct." PhRMA Br. 12. But that is equally true here. The illegal conduct in this case is the introduction of drugs and medical devices into interstate commerce with the intent that those products be used in a manner that the FDA has not approved. Just as the speech in Pittsburgh Press was evidence of illegal discrimination and the speech in Mitchell was evidence of unlawful racial animus, the speech at issue here is evidence of an intent to illegally distribute FDA-regulated products for unapproved uses.

The FDCA makes it illegal for a manufacturer to distribute an approved drug for an unapproved use. The core provision governing the FDA's regulation of drugs is the premarket approval requirement applicable to all "new drugs." 21 U.S.C. § 355. Specifically, the FDCA requires manufacturers to submit applications to the agency establishing that their new drugs are "safe for use" and "effective in use." See 21 U.S.C. § 355(b)(1)(A). The FDA can approve a new drug application only if the manufacturer has provided substantial evidence that the new drug will "have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling," 21 U.S.C. § 355(d)(5).<sup>2</sup> Except as provided in the FDAMA, it is illegal for

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<sup>2</sup>The term "labeling" is very broad and includes both the "label" of the drug or device and related promotional material, including reprints of journal articles and textbooks disseminated by manufacturers to potential customers. See 21 C.F.R. § 202.1(1)(2) (including "reprints" within the definition of "labeling" for purposes of 21 U.S.C. § 321(m)); see also United States v. Urbuteit, 335 U.S. 355, 357-58 (1948); United States v. Kordel, 335 U.S. 345, 349-50 (1948); United States v. Articles of (continued...)

the manufacturer to distribute a new drug in interstate commerce without first complying with these requirements. See 21 U.S.C. §§ 331(d), 355(a).

Because the entire premarket approval process is predicated on a showing of safety and effectiveness with respect to particular intended uses, a drug that has previously been approved for one use constitutes a "new drug" for purposes of any additional intended uses that have not been proven safe and effective. That is expressly recognized in an FDA regulation that WLF has not challenged. See 21 C.F.R. § 310.3(h)(4) ("The newness of a drug may arise by reason (among other reasons) of \* \* \* [t]he newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body." (emphasis added)).

Congress has long required manufacturers to obtain FDA approval or clearance for every use for which a new drug or device is intended. See 21 U.S.C. §§ 331(a), (d), 351(f), 355, 360c(f)(1), 360e. Indeed, WLF and its amici apparently do not dispute that manufacturers may be prohibited from advertising their products for any uses that the FDA has not approved as safe and effective. Such advertisements would evidence the manufacturers'

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<sup>2</sup>(...continued)  
Drugs for Veterinary Use, 50 F.3d 497, 500-01 (8th Cir. 1995); United States v. Diapulse Manufacturing Corp. of America, 389 F.2d 612, 616 (2d Cir.), cert. denied, 392 U.S. 907 (1968).

unlawful intent to distribute those products for the unapproved use. See Opening Br. 29-30. Thus, the manufacturer of a drug that has been approved for the treatment of AIDS (or even headaches) may not promote that drug for use in treating cancer. Before doing so, the manufacturer would have to demonstrate that the drug is safe and effective for cancer treatment and to obtain FDA approval for that particular use. See 21 U.S.C. § 355(b)(1)(A), (d)(5). Even where there is a published article in a peer-reviewed medical journal discussing the effectiveness of the drug in treating cancer, the manufacturer cannot refer to the article in an advertisement without evidencing a new intended use for the drug and thereby triggering the FDCA's approval requirements. See 21 C.F.R. § 201.128. Similar requirements apply to devices. See 21 U.S.C. §§ 351(f), 360e(c)(1)(A), (d)(2)(A), (B); 21 C.F.R. § 801.4.

Drug and device manufacturers are not only aware of this rule, they comply with it. Importantly, there is no meaningful legal distinction between advertising an unapproved use and the conduct at issue in this case. Yet, if upheld, the district court's ruling would allow manufacturers to promote the unapproved uses of their approved drugs and medical devices to physicians through the distribution of journal articles and textbooks discussing those off-label uses. Given the nature of the prescription drug and device markets, the authority to distribute journal articles about off-label uses and to discuss those articles in advertisements promoting drugs and devices would provide manufacturers with an effective means of circumventing the FDCA's approval requirements.

Thus, in the AIDS drug example, it makes no difference whether the manufacturer expressly labels the drug for cancer treatment, advertises the drug for cancer treatment, or distributes a journal article supporting use of the drug for cancer treatment. In each case, the manufacturer's conduct is dispositive evidence that the drug is now "intended" for treatment of cancer, 21 U.S.C. § 321(g)(1); but in each case, the manufacturer has not obtained approval for distribution of that new drug, as required by 21 U.S.C. § 355. The same analysis applies to medical devices. See 21 U.S.C. §§ 321(h), 360e(c)(1)(A), (d)(2).

Indeed, this example highlights another flaw in the arguments of WLF and its amici. Even WLF does not contend that a manufacturer could label its products for an unapproved use. But there is no principled distinction for First Amendment purposes between a manufacturer's speech on a label and a manufacturer's unsolicited dissemination of off-label information in a medical journal or textbook. In both cases, the manufacturer has used speech to further an illegal end.

PhRMA's position is fundamentally at odds with one of the basic purposes of the FDCA. Congress specifically amended the definition of "new drug" in 1962 to ensure that drug manufacturers would be required to demonstrate the effectiveness of their products for each condition prescribed in the labeling. See 21 U.S.C. §§ 321(p)(1), 355(d)(5), (e)(3); S. Rep. No. 87-1744, reprinted in 1962 U.S.C.C.A.N. 2884, 2898, 2901-02 (views of Sen.

Kefauver, et al.); see also Weinberger v. Hynson, Westcott and Dunning, Inc., 412 U.S. 609, 613, 630 (1972).

As the principal sponsor of the relevant provisions of the 1962 amendments (and certain of his colleagues) emphasized:

On what logical basis can one possibly argue that the initial claim for a drug, say the relief of headaches, should be supported by "substantial evidence," but that successive claims, for instance the cure of acne, need not be so supported? That consideration which would warrant examination and approval of the initial claim would be just as appropriate and compelling for successive claims. \* \* \*

With the benefit of this loophole the expectation would be that the initial claim would tend to be quite limited, which, of course, would expedite approval of the new drug application. Thereafter, "the sky would be the limit" and extreme claims of any kind could be made, subject only to the very cumbersome power of the FDA to seize a single specific shipment of the drug as misbranded.

S. Rep. No. 87-1744, reprinted in 1962 U.S.C.C.A.N. at 2901 (views of Sen. Kefauver, et al.); see also H.R. Rep. No. 94-853, at 14-15 (1976) (expressing intent that where a "particular device is intended to be used for more than one purpose \* \* \* \* each use may, at the Secretary's discretion, be treated as constituting a different device for purposes of classification and other regulation").

Thus, PhRMA's contention (PhRMA Br. 13 n.6) that the FDCA does not prohibit a drug manufacturer from distributing a drug for a new use as long as the FDA previously approved the drug for a prior use is flatly wrong. As explained above, the FDCA plainly does require manufacturers to demonstrate the effectiveness of their drugs for all intended uses before they are distributed for those uses.

See 21 U.S.C. §§ 331(d), 355(b)(1)(A), (d)(5); see also 108 Cong. Rec. 17,366 (Aug. 23, 1962).<sup>3</sup>

If PhRMA's position were correct, the "loophole" that Senator Kefauver identified in the 1962 legislative history would be a mile wide: a drug previously approved for treating acne could be distributed for the treatment of cancer, even though the manufacturer had not demonstrated that the drug was safe and effective for that new use. The manufacturer then would be able to encourage and profit from the widespread off-label use of the product, and would have little incentive to demonstrate that the product is safe and effective for such use. That extraordinary position, which, insofar as we are aware, the drug industry has not previously advocated, would cripple the FDA's ability to ensure that new drugs are effective for their intended uses. It would also place the public at the mercy of drug and device entrepreneurs. See United States v. Rutherford, 442 U.S. 544, 558 (1979). In sum, PhRMA's position is contrary to the FDCA, the agency's regulations, and sound public policy, and it has no support in the case law.

PhRMA also incorrectly contends (PhRMA Br. 12) that, under the government's view of the FDCA, "it is the speech and speech alone that renders the otherwise lawful sale of a drug illegal." The

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<sup>3</sup>As one commentator has explained, "[a]ny change in the recommended conditions of use, relating to such aspects as \* \* \* the indications for use, requires \* \* \* the approval of a Supplemental [New Drug Application] before marketing." Peter Barton Hutt, Regulation of the Practice of Medicine Under the Pure Food and Drug Laws, 33 Association of Food & Drug Officials of the United States Quarterly Bulletin 3, 12 (Jan. 1969).

speech does not "render" the sale of a drug unlawful; rather, the speech furnishes evidence of the manufacturer's unlawful intent to distribute the drug for a new intended use that the FDA has not approved as safe and effective. And the Supreme Court has made clear that "[t]he First Amendment \* \* \* does not prohibit the evidentiary use of speech \* \* \* to prove motive or intent." Wisconsin v. Mitchell, 508 U.S. at 489.<sup>4</sup>

c. WLF (Br. 25, 38-39) repeatedly attempts to analogize the FDCA's treatment of the dissemination of off-label information to the use of the statement "go buy a gun" as evidence of a crime. The analogy is wholly inapt. As WLF notes, the ambiguous statement "go buy a gun" can carry a perfectly lawful message. Here, by contrast, a manufacturer's unsolicited dissemination to physicians of information about the off-label uses of their products can have only one plausible explanation: the manufacturer intends to encourage the physicians to prescribe their products for the off-label uses even though the manufacturer has not demonstrated that the unapproved uses are safe and effective. Because Congress has prohibited the distribution of drugs and medical devices for an

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<sup>4</sup>Although PhRMA suggests otherwise (PhRMA Br. 12), a manufacturer's continued distribution of a drug or device with the knowledge that the product is subject to widespread off-label use could demonstrate that the manufacturer intends to distribute the product for that off-label use. See 21 C.F.R. § 201.128; 21 C.F.R. § 801.4; see also H.R. Rep. No. 94-853, at 14; 37 Fed. Reg. 16,504 (Aug. 15, 1972). The dissemination of off-label information is just one type of evidence that can be used to demonstrate a manufacturer's unlawful intent. As this Court has recognized, the "intended use" of a product is determined "from its label, accompanying labeling, promotional claims, advertising, and any other relevant source." Action on Smoking and Health v. Harris, 655 F.2d 236, 239 (D.C. Cir. 1980).



unapproved use, it can also prohibit the dissemination of information that would promote such unlawful distribution. See Pittsburgh Press, 413 U.S. at 388-89.<sup>5</sup>

d. PhRMA erroneously contends (PhRMA Br. 13-14) that Pearson v. Shalala, 164 F.3d 650 (D.C. Cir. 1999), "inherently rejects" our argument here. Until filing its petition for rehearing in Pearson, the government did not argue in this Court that the statutory scheme at issue there involved the regulation of illegal commercial activity along the lines permitted under such cases as Mitchell and Pittsburgh Press, and the panel did not address the issue in its opinion. See Pearson v. Shalala, 172 F.3d 72, 72-73 (D.C. Cir. 1999) (Silberman, J., concurring in denial of rehearing en banc). The subsequent denial of rehearing does not preclude the government from litigating the issue in this case. See United States v. North, 920 F.2d 940, 950 (D.C. Cir. 1990), cert. denied, 500 U.S. 941 (1991).<sup>6</sup>

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<sup>5</sup>Contrary to WLF's suggestion (WLF Br. 25 n.10), the FDAMA does not preclude a manufacturer from disseminating information to dissuade physicians from using its products in an unapproved manner. The purpose of the FDAMA is to ensure that manufacturer promotion of off-label uses is unbiased, balanced, and ultimately substantiated by scientific evidence. See, e.g., 21 U.S.C. §§ 360aaa-3, 360aaa-6(a), (b). Although the FDAMA precludes a manufacturer from disseminating information to ensure that physicians are prescribing a drug for an off-label use in a "proper manner" (WLF Br. 25 n.10), that result makes sense, because such dissemination would constitute evidence that the manufacturer intends that the product be used for an unapproved purpose.

<sup>6</sup>Moreover, the Court in Pearson recognized that "[d]rugs \* \* \* appear to be in an entirely different category" than the dietary supplements at issue in that case because "the potential harm presumably is much greater." Id. at 656 n.6.

This case is also very different from 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484 (1996). In 44 Liquormart, the State attempted to justify a ban on certain liquor advertising based on its unexercised power to "ban the sale of alcoholic beverages outright." 517 U.S. at 508. Thus, the State in that case did not actually ban the sale of alcoholic beverages; it only banned speech. Here, by contrast, Congress has actually exercised its power to make unlawful the distribution of drugs and devices for unapproved new uses, and the speech regulated under the FDAMA is manifest evidence of that unlawful conduct. Thus, this case is governed by Pittsburgh Press, which was distinguished and cited with approval in 44 Liquormart. See 517 U.S. at 497 n.7 (plurality opinion). Moreover, the information at issue in this case is far more susceptible to manipulation and, if biased or incomplete, could have far more dangerous consequences for the public than the objective and easily evaluated retail price information that was banned from advertising in 44 Liquormart.

2.a. WLF does not challenge the district court's ruling (J.A. 806) that the FDAMA's supplemental application requirement directly and materially advances the government's interest in encouraging manufacturers to undertake the scientific studies and to perform the other steps necessary to obtain FDA approval for the off-label uses of their products.

WLF and its amici contend, however, that the government's additional interest in preventing manufacturers from selectively disseminating favorable off-label information to physicians is not

"substantial" in light of its alleged paternalistic character. But the FDAMA was not enacted to keep physicians ignorant of truthful information about off-label uses. To the contrary, the statute applies only to manufacturers and only with respect to products in which they have a commercial interest.

Moreover, the FDAMA does not interfere with the treatment decisions of physicians. Rather, it ensures that physicians can make their own independent treatment decisions on the basis of complete and accurate information. As the district court recognized, absent regulation, "manufacturers will likely only seek to disseminate information that presents their product in a favorable light." J.A. 752 (13 F. Supp. 2d at 65). And if off-label uses are as prevalent as WLF suggests, the need for physicians to receive unbiased and complete information in making their treatment decisions is particularly strong.

Our system of regulating drugs and devices is premised on the principle that there is a legitimate government and public health interest in ensuring that information about such products is accurate. Indeed, that is why Congress established an expert agency to evaluate the complex scientific data for each new intended use of a drug or device before allowing the product to be distributed for such use. The FDA has the resources and relevant expertise to evaluate the data to determine whether a particular use is safe and effective; individual physicians generally do not.

Thus, the FDAMA encourages manufacturers to perform the scientific studies necessary for the FDA to make those judgments,

and it enables physicians to treat their patients with the benefit of full disclosure of relevant data by manufacturers seeking to promote the off-label uses of their products. As explained in our opening brief (at 43), the Supreme Court and this Court have recognized the validity of interests that are no less "paternalistic" than the interests at issue in this case. See, e.g., Rubin v. Coors Brewing Co., 514 U.S. 476, 485 (1995) (recognizing government's "significant interest in promoting the health, safety, and welfare of its citizens."); Edenfield v. Fane, 507 U.S. 761, 769 (1993) ("there is no question that [the government's] interest in ensuring the accuracy of commercial information in the marketplace is substantial"); Pearson, 164 F.3d at 656.

b. WLF does not contest our showing that the FDAMA directly and materially advances the interest in preventing manufacturers from disseminating biased information to physicians. See Opening Br. 41-43, 45-46. However, WLF and its amici present a decidedly incomplete view of the benefits and risks of off-label uses of drugs and medical devices and the FDA's position with respect to such unapproved uses. As explained in our opening brief (at 44), the FDA has recognized that off-label uses occur and that they can be beneficial in certain circumstances. But there is good reason why Congress has required manufacturers to demonstrate the safety and effectiveness of the uses of their products when they are to be commercially distributed for those uses. As the record below also demonstrates, the risk to the public from unproven uses of drugs and devices is both real and substantial. See J.A. 523-24, 527-36,

594-95. Patients can be directly harmed by the drug or device, or an ineffective drug or device might be used in place of another drug or device that has been approved for the particular condition, thereby depriving the patient of an effective treatment. See J.A. 523-24, 637-38; see also United States v. Rutherford, 442 U.S. at 557.

3. As explained in our opening brief (at 46-52), the FDAMA is a narrowly tailored means of accomplishing substantial congressional objectives. WLF nevertheless suggests (WLF Br. 32) that Congress could have accomplished its objective of encouraging manufacturers to seek approval of off-label uses by extending the period under which their drugs are protected from competition. Another provision of the FDAMA does extend by six months the period of market exclusivity for certain approved drugs if the manufacturer conducts studies requested by the FDA to evaluate the safety and effectiveness of certain off-label pediatric uses of those drugs. See 21 U.S.C. § 355a(a), (c). Thus, Congress has adopted an alternative means of encouraging manufacturers to obtain approval of off-label uses in the pediatric area, where off-label uses are particularly prevalent, see J.A. 727, and the need for adequate studies is particularly compelling.

Congress was not required similarly to extend the period of exclusivity for all other drugs. Indeed, such action would have undermined Congress's competing interest in promoting competition in the drug industry, which Congress has furthered by enacting provisions of the FDCA that allow low-cost generic drugs to enter

the market through an abbreviated approval process. See Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984); Teva Pharmaceuticals, U.S.A., Inc. v. United States Food and Drug Administration, 182 F.3d 1003, 1004 (D.C. Cir. 1999). Congress was not required to undermine those provisions by extending the period of exclusivity for all drugs for which approval of off-label uses is sought. In any event, exclusivity is an imperfect device for encouraging manufacturers to seek approval of off-label uses because many drugs already have generic competition.

4. Contrary to the contentions of WLF (Br. 40-41) and the American Civil Liberties Union ("ACLU") (Br. 1-20), the district court correctly concluded that the FDAMA regulates commercial speech rather than pure speech. The FDAMA applies only to the dissemination of off-label information by manufacturers proposing commercial transactions. The FDAMA in no way restricts the exchange of information among scientists, researchers, physicians, or members of the general public. Even with respect to manufacturers, the FDAMA applies only to the unsolicited dissemination of off-label information. Thus, the FDAMA expressly provides that it shall not be construed as prohibiting a manufacturer from disseminating such information in response to a physician's unsolicited request. See 21 U.S.C. § 360aaa-6(a).

The contention of the ACLU (Br. 10) that the FDAMA and the challenged FDA Guidance Documents "broadly preclude manufacturers from virtually any comment on an issue of public importance" is

also inaccurate. The statute and Guidance Documents apply only to the manufacturers' promotion of unlawful commercial transactions. And it is difficult to discern how a manufacturer could "strip all commercial features" (ACLU Br. 13) from its unsolicited dissemination of information about the off-label uses of its drugs and devices to the physicians who prescribe those products.

5. As explained in our opening brief (at 52-54), the district court also erred in holding that the FDA's Guidance Document governing manufacturer support of scientific and educational activities violates the First Amendment. WLF's treatment of that issue warrants no additional response.

#### CONCLUSION

For the foregoing reasons, the judgment of the district court should be reversed.

Respectfully submitted,

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NOVEMBER 1999

**CERTIFICATE OF SERVICE**

I hereby certify that on this 22d day of November, 1999, I filed and served the foregoing Reply Brief for the Appellants by causing an original and 15 copies to be delivered by hand to the Clerk of the Court and by further causing two copies to be delivered to the following in the manner specified:

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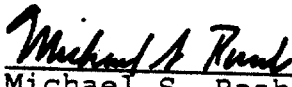
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# **CERTIFICATE OF COMPLIANCE**

Pursuant to Fed. R. App. P. 32(a)(7)(C), I hereby certify that, excluding the portions exempted by Fed. R. App. P. 32(a)(7)(B)(iii) and D.C. Cir. R. 32(a)(2), this brief complies with the applicable type-volume limitations; it contains 5,209 words as counted by Corel WordPerfect 7, the word-processing software used to prepare this brief.

  
\_\_\_\_\_  
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**DRUG PRICE AND PATENT TERM ACT**  
P.L. 98-417

**DRUG PRICE COMPETITION AND PATENT  
TERM RESTORATION ACT**

*P.L. 98-417, see page 98 Stat. 1585*

**Senate Report (Judiciary Committee) No. 98-547,  
June 26, 1984 [To accompany S. 1538]**

**House Report (Energy and Commerce Committee) No. 98-857(I),  
June 21, 1984 [To accompany H.R. 3605]**

**House Report (Judiciary Committee) No. 98-857(II),  
Aug. 1, 1984 [To accompany H.R. 3605]**

**Cong. Record Vol. 130 (1984)**

**DATES OF CONSIDERATION AND PASSAGE**

**Senate June 29, August 10, September 12, 1984**

**House September 6, 1984**

**S. 1538 was passed in lieu of the House bill after amending its language to contain the text of the House bill. The House Report (Part I, this page, and Part II, page 2686) and a Related Report (page 2721) are set out.**

**HOUSE REPORT NO. 98-857, Part I**

**[page 1]**

**The Committee on Energy and Commerce, to whom was referred the bill (H.R. 3605) to amend the Federal Food, Drug, and Cosmetic Act to authorize an abbreviated new drug application under section 505 of that Act for generic new drugs equivalent to approved new drugs, having considered the same, report favorably thereon with amendments and recommend that the bill as amended do pass.**

\* \* \* \* \*

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**PURPOSE AND SUMMARY**

**TITLE I**

**The purpose of Title I of the bill is to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962. Under current law, there is a generic drug approval procedure for pioneer drugs approved before 1962, but not for pioneer drugs approved after 1962.**

**Title I of the bill generally extends the procedures used to approve generic copies of pre-62 drugs to post-62 drugs. Generic copies**

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of any drugs may be approved if the generic is the same as the original drug or so similar that FDA has determined the differences do not require safety and effectiveness testing.

Title I also requires patent owners to submit information to FDA regarding produce and use patents that cover approved drugs. Generic copies of these drugs may be approved when the patents expire unless the generic company certifies that the patent is invalid or will not be infringed. In such cases, the generic company must notify the patent owner about its certification and approval of the generic drug may not be made effective until the court decides the suit for patent infringement or a period of 18 months, whichever occurs first. Notification must be given when the generic has submitted an ANDA with bioequivalence data.

In addition, Title I affords four years of exclusive market life to drugs which may not be patented and which are approved for the first time after enactment of the bill. Further, drugs which were approved for the first time between 1982 and the date of enactment received ten years of exclusive market life.

### TITLE II

The purpose of Title II of the bill is to create a new incentive for increased expenditures for research and development of certain products which are subject to premarket government approval. The incentive is the restoration of some of the time lost on patent life while the product is awaiting pre-market approval. Under current law, a patent continues to run while the maker of the product is testing and awaiting approval to market it.

Title II of H.R. 3605 provides for one extension of the earliest patent on certain products subject to pre-market approval. The extension would be for a period equal to: (1) half of the time required to test the product for safety (and effectiveness in some cases); and (2) all of the time required for the agency to approve marketing of the product. These products include: human drugs, animal drugs, medical devices, and food and color additives.

Title II places several limits on the period of patent extension. First, the period of extension may not exceed two years for products either currently being tested or awaiting approval. For all other products, the period of extension may not exceed five years. Second, the period of patent extension when added to the patent time left after approval of the product may not exceed fourteen years. Third, any time that the product's manufacturer did not act with due diligence during the regulatory review period would be subtracted.

Finally, Title II provides that it is not an act of patent infringement for a generic drug maker to import or to test a patented drug in preparation for seeking FDA approval if marketing of the drug would occur after expiration of the patent.

### HEARINGS

The Committee's Subcommittee on Health and the Environment held one day of hearings on H.R. 3605, the Drug Price Competition Act, on July 15, 1983. Testimony was received from 15 witnesses,

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representing nine organizations, with additional material submitted by two individuals and organizations.

### COMMITTEE CONSIDERATION

On August 2, 1983, the Committee's Subcommittee on Health and the Environment met in open session and ordered favorably reported H.R. 3605 without amendment by voice vote. On June 12, 1984, the Committee met in open session on H.R. 3605, amended the bill, and ordered it favorably reported by a voice vote. The title of the bill, as amended, is the "Drug Price Competition and Patent Term Restoration Act of 1984."

### BACKGROUND AND NEED FOR THE LEGISLATION

#### TITLE I—ABBREVIATED NEW DRUG APPLICATIONS

Prior to 1962, the Federal Food, Drug and Cosmetic Act (FFDCA) required that all drugs be approved as safe before they could be marketed. The 1962 amendments required that all new drugs, generic and pioneer, must be approved as safe and effective prior to marketing.

As a result of the 1962 amendments, FDA did two things regarding pre-1962 drugs. First, the agency created the Drug Efficacy Study (DESI) to determine if all pre-1962 drugs were effective. Second, FDA established a policy permitting the approval of a generic drug equivalent to a safe and effective pre-1962 pioneer drug.

As a result of the 1962 amendments, the manufacturer of a pioneer drug must conduct tests on humans that show the product to be safe and effective and submit the results in a new drug application (NDA). A manufacturer of a generic drug must conduct tests that show the generic drug is the same as the pioneer drug and that it will be properly manufactured and labeled. This information is submitted in an abbreviated new drug application (ANDA).

The only difference between a NDA and an ANDA is that the generic manufacturer is not required to conduct human clinical trials. FDA considers such retesting to be unnecessary and wasteful because the drug has already been determined to be safe and effective. Moreover, such retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective.

The FDA allows this ANDA procedure only for pioneer drugs approved before 1962. There is no ANDA procedure for approving generic equivalents of pioneer drugs approved after 1962. While the FDA has been considering since 1978 an extension of the pre-1962 ANDA policy to post-1962 drugs, it has not extended the regulation. Because of the agency's failure to act, Title I of H.R. 3605 is necessary to establish a post-1962 ANDA policy.

Some have suggested that "Paper NDAs" be used to approve generic equivalents of pioneer drugs approved after 1962. Under the Paper NDA procedure, the generic manufacturer may submit scientific reports, instead of clinical trials, to support findings of safety and efficacy. This procedure is inadequate, however, because FDA estimates that satisfactory reports are not available for 85 percent of all post-1962 drugs.

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Currently, there are approximately 150 drugs approved after 1962 that are off patent and for which there is no generic equivalent. All of these drugs could be approved in generic form if there was a procedure. Each year, more pioneer drugs go off patent and become available for approval as generics.

Among the drugs available or soon to be available for generic approval are five best sellers: valium, motrin, inderal, dyazide, and lasix. Dyazide, for example, is the most widely used diuretic for the treatment of high blood pressure. Its patent expired in 1981. Valium is a popular tranquilizer whose patent expires in 1985. Another drug whose patent has expired is indocin, an anti-inflammatory drug used in the treatment of arthritis that is the tenth highest selling drug in the United States.

The availability of generic versions of pioneer drugs approved after 1962 would save American consumers \$920 million over the next 12 years. Older Americans, in particular, would benefit because they use almost 25 percent of all prescription drugs.

Moreover, the lack of generics for post-1962 pioneer drugs will cost Federal and State governments millions of dollars. For the drug metronidazole, purchased by the Department of Defense, the taxpayers saved approximately \$1.2 million in one year as a result of the availability of a lower priced generic version. Federal and State governments will be denied comparable savings on drugs approved after 1962 because of the lack of an approval procedure.

### TITLE II—PATENT TERM RESTORATION

Patents are designed to promote innovation by providing the right to exclude others from making, using, or selling an invention. They enable innovators to obtain greater profits than could have been obtained if direct competition existed. These profits act as incentives for innovative activities.

Although the patent term in the United States is 17 years, the period during the patent term in which products are marketed (the effective patent term) is usually less than 17 years because patents often are obtained before products are ready to be marketed.

Effective patent terms are influenced by many factors, including Federal pre-marketing and premanufacturing regulations. The products covered by these regulations include pharmaceuticals, medical devices, food additives, and color additives. Pharmaceuticals for instance cannot be marketed in the United States until they have been approved by the Food and Drug Administration (FDA). To obtain such approval, drugs must undergo extensive testing to prove they are both safe and effective. All these products are subject to different regulations that have had varying impacts on effective patent terms.

In testimony before several Congressional committees, representatives from the pharmaceutical firms that are heavily involved in basic research and rely upon patents, claimed that the average effective patent term of drugs has declined. They argued that a continuation of the decline would result in decreased expenditures for research and development and, eventually, in a decline in the introduction of new drugs.

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As compensation for the loss of patent term due to government review, the research intensive firms argued for patent term extension legislation. They stated that the legislation would create a significant, new incentive which would result in increased expenditures for research and development, and ultimately in more innovative drugs.

### COMMITTEE OVERSIGHT FINDINGS

Pursuant to clause 2(1)(3)(A) of Rule XI of the Rules of the House of Representatives, the Committee reports that oversight of the Food and Drug Administration and the Federal Food, Drug, and Cosmetic Act was conducted by the Subcommittee on Health and the Environment. A hearing was held on July 15, 1983. The findings of the Committee's oversight activities have been incorporated into the legislation and are discussed in those portions of this report entitled "Background and Need for the Legislation" and "Section-by-Section Analysis."

### COMMITTEE ON GOVERNMENT OPERATIONS

Pursuant to clause 2(1)(3)(D) of rule XI of the Rules of the House of Representatives, no oversight findings have been submitted to the Committee by the Committee on Government Operations.

### COMMITTEE COST ESTIMATE

In compliance with clause 7(a) of rule XIII of the Rules of the House of Representatives, the Committee believes that the costs, if any, incurred in carrying out H.R. 3605 will be offset by savings to the Federal government. In testifying before the Committee's Subcommittee on Health and the Environment, officials from the Food and Drug Administration estimated that any greater workload resulting from the approval of generic drugs under Title I would be absorbed initially. Later, the officials estimated, some additional staff might be required to process generic drug applications. This additional staff could cost up to \$1.1 million. The actual cost to the Federal government cannot be estimated because it is unknown how much additional staff, if any, might be hired.

Enactment of the legislation, however, will result in significant cost savings to the Federal government. Unlike the costs of H.R. 3605, these savings are certain. The Federal government spent about \$2.4 billion for drugs in 1983. Many of these drugs will be available as low cost generic after enactment of H.R. 3605. For example, the Department of Defense saved approximately \$1.2 million in one year when a lower priced generic version of metronidazole became available.

### CONGRESSIONAL BUDGET OFFICE ESTIMATE

Pursuant to clauses 2(1)(3) (B) and (C) of rule XI of the Rules of the House of Representatives, the Committee sets forth the following letter and cost estimate prepared by the Congressional Budget Office with respect to the reported bill:

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U.S. CONGRESS,  
CONGRESSIONAL BUDGET OFFICE,  
Washington, DC, June 19, 1984.

Hon. JOHN D. DINGELL,  
*Chairman, Committee on Energy and Commerce,  
House of Representatives, Washington, DC.*

DEAR MR. CHAIRMAN: The Congressional Budget Office has reviewed H.R. 3605, the Drug Price Competition and Patent Term Restoration Act of 1984, as ordered reported by the House Committee on Energy and Commerce on June 12, 1984.

Title I of this bill would allow drug manufacturers to use an abbreviated new drug application (ANDA) when seeking approval to make generic copies of drugs that were approved by the Food and Drug Administration (FDA) after 1962. An estimated 150 drug products approved after 1962 are currently off patent and would become available for generic copy using the ANDA procedure proposed in this bill.

The FDA estimates that the enactment of H.R. 3605 would at least triple the workload of the division responsible for approving ANDAs. Currently, this division reviews ANDAs for generic copies of pre-1962 approved drug products. The workload would increase as several manufacturers file an ANDA for each drug product that becomes available for generic copy. Because they would be reviewing information on new drugs, the FDA believes it would take them a year to process each of the new applications. This is about three months longer on average than it currently takes to process a pre-1962 ANDA. Dr. Marvin Seife, Director of FDA's Division of Generic Drug Monographs, testified before the Subcommittee on Health and the Environment that a greater workload could at first be absorbed, but may later require additional office space and 15 new FDA employees. Assuming an average full-time equivalent position plus overhead and fringe benefits is \$70,000, the potential cost to the FDA of implementing this legislation could be about \$1.1 million. The actual cost to the federal government would depend on the extent to which the FDA would expand to accommodate the increased workload.

Enactment of this legislation could also result in savings to both the federal and state and local governments. In fiscal year 1983, the federal government spent approximately \$2.4 billion for drugs in the Medicaid program, and in veteran and military hospitals. Data on drug costs in the Medicare program are unavailable. If the federal government is currently purchasing these 150 copiable drug products at higher, brand name prices, savings may result if lower priced, generic copies of these drugs are substituted.

It is difficult to know in advance which of the available 150 drug products manufacturers would choose to copy. It is also difficult to estimate the price at which these generic copies would be sold. Generic versions of ten popular drug products show their price to be on average 50 percent less than their brand name equivalent. The dollar amount the federal government currently spends on these 150 brand name drug products is unknown.

Title II of this bill would extend the amount of time for which certain patents are issued to include some or all of the time re-



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quired for a manufacturer to test a product for safety and efficacy and to receive marketing approval. Products affected by this legislation would be drugs, medical devices, and food and color additives. Manufacturers must show due diligence in their product testing or this amount of time will be subtracted from the total life of the patent. This provision would place an additional burden on the FDA. They would be responsible for keeping track of a manufacturer's product testing time and for determining their diligence in completing the testing. These costs, however, would be negligible.

Enactment of this bill could result in increased personnel costs to the federal government of approximately \$1.1 million. The bill, however, does not specifically authorize additional appropriations for the FDA. This bill may also result in savings if cheaper, generic drugs are made available for purchase by the federal government. These savings would occur in various programs throughout the budget such as Medicare, Medicaid, and the Veterans Administration. However, the magnitude of these savings is unknown.

Please call me if I can be of additional assistance, or your staff may wish to contact Carmela Pena (226-2820) of our Budget Analysis Division for further details on this estimate.

Sincerely,

ERIC HANUSHEK  
(For Rudolph G. Penner, Director).

### INFLATIONARY IMPACT STATEMENT

Pursuant to clause 2(1)(4) of rule XI of the Rules of the House of Representatives, the Committee makes the following statement with regard to the inflationary impact of the reported bill:

The Committee believes that enactment of H.R. 3605 will not have an inflationary impact upon the economy. In fact, Title I of the bill will have a deflationary effect because it makes available lower priced generic versions of drugs. Such generic drugs are three to fifteen times less costly than their brand name counterparts. The estimated \$1 billion cost savings to consumers as a result of Title I's generic drug approval procedure will have a deflationary effect upon the national economy. While Title II of the bill provides for a limited extension of the patents on certain products, the Committee believes that the additional patent term will act as a spur to develop innovative and, ultimately, less costly treatments for diseases.

### SECTION-BY-SECTION ANALYSIS

#### TITLE I—DRUG PRICE COMPETITION ACT

##### Section 101

Section 101 amends section 505 of the Federal Food, Drug and Cosmetic Act (FFDCA)<sup>1</sup> to establish a new subsection (J) providing for the approval of abbreviated new drug applications (ANDA). Paragraph (1) of subsection (j) sets forth the information which must be included in an ANDA.

<sup>1</sup> 21 U.S.C. 355.

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### *ANDA's for drugs which are the same*

In the case of drugs which are the same as the listed drug, the focus of the bill is to provide the Food and Drug Administration (FDA) with sufficient information to assure that the generic drug is the same as the listed drug<sup>2</sup> that has previously been determined to be safe and effective. Some have suggested that a generic drug must be identical in all respects to the listed drug instead of the same. The regulations that permit ANDA's for pre-1962 pioneer drugs make no such distinction.<sup>3</sup> In rejecting the use of the term identical, the FDA regulation comments that "identical means a product that is the same in dosage form, strength, and route of administration, contains the same active ingredient, and is recommended for use under the same conditions of use."<sup>4</sup> The Committee has adopted the FDA's policy of utilizing the term "same" except that the bill permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved as explained below.

First, an ANDA must include sufficient information to show that the conditions of use for which the applicant is seeking approval are the same as those that have been previously approved for the listed drug. The applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

While the FDA's current regulations for considering ANDA's for pioneer drugs approved before 1962 permit an applicant to petition for approval for an indication other than that which has been approved for the pioneer drug, section 101 of the bill overturns that policy.<sup>5</sup> Thus, an ANDA may not be considered for a condition of use that has not been previously approved for the listed drug.

An ANDA must also contain sufficient information to show that the active ingredients of the generic drug are the same as those of the listed drug. If the listed drug has one active ingredient, then the active ingredient of the generic must be the same. If the listed drug has more than one active ingredient, then sufficient information must be included to show that all of the active ingredients in the generic drug are the same.

In addition, an ANDA must contain sufficient information to show that the route of administration, the dosage form and the strength of the generic drug are the same as those of the listed drug.

Further, an ANDA must include sufficient information to show that the generic drug is bioequivalent to the listed drug.

<sup>2</sup> The term "listed drug" is explained in paragraph (6) of new section 505(j) of the FDCA. Generally, a listed drug includes any drug that has been approved for safety and effectiveness or that has been approved under new subsection (j).

<sup>3</sup> 48 Fed. Reg. 2751 (1983).

<sup>4</sup> Id. at 2753.

<sup>5</sup> Id. at 2755.

21 C.F.R. 314.2(c) provides in part:

"A prospective applicant may seek a determination of the suitability of an abbreviated new drug application for a product that the applicant believes similar or related to a drug product that has been declared to be suitable for an abbreviated new drug application . . ."

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Fifth, an ANDA must contain adequate information to show that the proposed labeling for the generic drug is the same as that of the listed drug. The Committee recognizes that the proposed labeling for the generic drug may not be exactly the same. For example, the name and address of the manufacturers would vary as might the expiration dates for the two products. Another example is that one color is used in the coating of the listed drug and another color is used in that of the generic drug. The FDA might require the listed drug maker to specify the color in its label. The generic manufacturer, which has used a different color, would have to specify a different color in its label.

Sixth, an ANDA must include a list of all the components of the generic drug, a description of the composition of the generic drug, a description of the methods and controls used in the manufacture, processing and packing of the generic drug, samples of the generic drug and its components, and specimens of the proposed labeling.

Seventh, an ANDA must include a certification by the applicant regarding the status of certain patents applicable to the listed drug if the patent information has been submitted under section 505 (b) or (c). With respect to all product patents which claim the listed drug and all use patents which claim an indication for the drug for which the applicant is seeking approval (hereafter described as a controlling use patent), the applicant must certify, in his opinion and to the best of his knowledge, as to one of four circumstances.

The applicant may certify that the patent information required under sections 505 (b) and (c) has not been submitted if that is the case. If appropriate, the applicant may certify that one or more of the product or controlling use patents provided have expired. Third, the applicant may certify when appropriate that one or more of the product or controlling use patents will expire at some specified date in the future. When the applicant makes these certifications, it must rely upon the patent information supplied to the FDA. Last, an applicant may certify if applicable that one or more of the product or controlling use patents are invalid or will not be infringed.

The Committee recognizes that in some instances an applicant will have to make multiple certifications with respect to product or controlling use patents. For example, if the product patent has expired and a valid controlling use patent will not expire for three years, then the applicant must certify that one patent has expired and the other will expire in three years. The Committee intends that the applicant make the appropriate certification for each product and controlling use patent.

Eighth, if there are indications which are claimed by any use patent and for which the applicant is not seeking approval, then an ANDA must state that the applicant is not seeking approval for those indications which are claimed by such use patent. For example, the listed drug may be approved for two indications. If the applicant is seeking approval only for indication No. 1, and not indication No. 2 because it is protected by a use patent, then the applicant must make the appropriate certification and a statement explaining that it is not seeking approval for indication No. 2.

Finally, the Committee intends that an ANDA contain any information available to the applicant regarding reports of adverse ef-

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fects not reflected in the labeling, an environmental impact analysis pursuant to FDA regulations, statements regarding the protection of human subjects in clinical investigations as required by FDA regulations, and a statement regarding compliance with good laboratory practices in non-clinical investigations as required by FDA regulations.<sup>6</sup>

### *ANDA's for drugs which are different*

Paragraph (2)(C) prohibits any person from submitting an ANDA for a generic drug which differs from the listed drug unless the change is permitted by the statute and the FDA has granted a petition requesting the change.

If an applicant wishes to vary the route of administration, dosage form or strength of the generic drug from the listed drug, it must first petition the FDA for permission to file an ANDA for the differing generic drug. In addition, an applicant may request to vary one of the active ingredients in the generic drug from the listed drug when the listed drug is a combination product. The remaining active ingredients of the generic drug must be the same as the other active ingredients of the listed drug.

These are the only changes from the listed drug for which an applicant may petition. As is explained in the ANDA regulations for pre-1962 drugs, the Committee generally expects that approval of petitions will "ordinarily be limited to dosage forms for the same route of administration or to closely related ingredients."<sup>7</sup> If the FDA grants a petition for a change from the listed drug, the FDA may require such additional information in the ANDA regarding the change as it deems necessary.

The FDA must approve a petition to submit an ANDA for a differing generic drug unless clinical studies are needed to show the safety and effectiveness of the change. In reviewing a petition to change one of the active ingredients in a combination product, the Committee does not intend to change the FDA's current policy regarding the evaluation of the safety and effectiveness of combination products. If the FDA finds that safety and effectiveness testing of the active ingredients of the drug, individually or in combination, is required, then the FDA must deny the petition.

The FDA must either approve or disapprove a petition within 90 days of its submission. As is the case under the current regulations, "there is no legal requirement that the hearing opportunity provided by section 505(c) be made available to ANDA applicants who disagree with an adverse agency decision" on whether clinical studies are needed to show the safety and effectiveness of the differing generic drug.<sup>8</sup> "Appropriate review of such decisions may be had . . . under the applicable standard—that applicable to administrative decisionmaking generally—which is whether the agency's decision is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law (5 U.S.C. 706(2)(A))."<sup>9</sup> If the FDA

<sup>6</sup> Id. at 2756. See 21 CFR 314.2(f) (4), (5), (6), (7), and (8).

<sup>7</sup> Id. at 2755. See 21 CFR 314.2(c).

<sup>8</sup> Id. at 2752.

<sup>9</sup> Id.

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does not approve a petition, then an ANDA may not be filed for a generic drug that varies from the listed drug.

An ANDA for a drug which differs from the listed drug and for which a petition has been approved by the FDA must contain such additional information regarding the difference as the FDA may require when it granted the petition. For example, if the route of administration of the generic drug differs from that of the listed drug, then the FDA may require such additional information on that change as it deems necessary.

If the FDA approves a petition permitting an applicant to vary one of the active ingredients of a generic drug from those of the listed combination drug, the ANDA must contain sufficient information to show that the active ingredients of the generic drug (including the varying active ingredient) are of the same pharmacological or therapeutic class as those of the listed drug. In addition, the differing generic drug must be expected to have the same therapeutic effect when administered to patients for an approved condition of use.

An example of such a change in one of the active ingredients that the FDA might find acceptable is the substitution of acetaminophen for aspirin in a combination product. Another example might be the substitution of one antihistamine for another. The active ingredient, which the applicant wishes to vary and which the FDA has granted a petition, must have been approved for safety and effectiveness or must not be within the requirements of section 201(p) of FFDCA.<sup>10</sup>

### *Certification of invalidity of noninfringement of a patent*

When an applicant certifies that any product or controlling use patent is invalid or will not be infringed, paragraph (2)(B) requires that it must give notice of such certification to either the owner of the patent or the representative of the patent owner that was designated when the patent information was submitted under section 505(b) or (c) of the FFDCA. The FDA may, by regulation, establish a procedure for designating in the NDA the representative of the patent owner. In addition, notice of the certification must be given to the holder of the approved New Drug Application (NDA) for the drug which is claimed by a product patent or the use of which is claimed by a use patent.

This notice must be given simultaneously with the submission of an ANDA. The Committee does not intend that applicants be permitted to circumvent this notice requirement by filing sham ANDA's or ANDA's which are substantially incomplete. The Committee intends that the applicant must have made a good faith effort to meet the requirements set forth in paragraph (2)(A) regarding the contents of an ANDA.

While the Committee does not intend that failure to include a minor piece of information in an ANDA vitiates the effectiveness of the notice required under paragraph (2)(B), an ANDA must in-

<sup>10</sup> 21 U.S.C. 321(p). For example, a drug marketed prior to 1938 and unchanged is a "grandfathered drug" and thus not within the scope of the definition of "new drug" set forth in section 201(p) of the FFDCA. Another example of a drug outside the scope of section 201(p) is a product that is generally recognized as safe and effective and that has been used to a material extent or for a material time.

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clude the results of any required bioavailability or bioequivalence tests. Failure to include the results of such tests when required will void the effectiveness of any notice under paragraph (2)(B). Notice must then be given again when an ANDA with any required bioavailability or bioequivalence data is submitted to the FDA.

When the applicant gives notice of the certification of patent invalidity or non-infringement, the notice must state that an ANDA has been submitted to obtain approval of the drug to engage in the commercial manufacture, use or sale of the generic drug before the expiration of the patent which has been certified as invalid or non-infringed.

If an ANDA is amended after submission to include a certification that a product patent or controlling use patent is invalid or not infringed, then the notice of such certification must be given to the appropriate parties when the amended application is submitted.

### *Grounds for disapproval of an ANDA*

Paragraph (3) provides that the FDA shall approve an ANDA except in one of the following circumstances.

First, the FDA shall not approve an ANDA if the methods used in, or the facilities and controls used for, the manufacture, processing and packing of the generic drug are inadequate to assure and preserve its identity, strength, quality and purity.

Second, an ANDA shall not be approved if it does not contain adequate information to show that each of the conditions for use for the generic drug have been previously approved for the listed drug. If an ANDA includes a condition for use for which the listed drug has not been approved, then the generic drug may not be approved.

Third, an ANDA must be disapproved if the active ingredient of the generic drug is not the same as that of the listed drug and the listed drug has only one active ingredient. An ANDA must also be disapproved if any of the active ingredients in the generic drug are not the same as those of the listed drug unless a petition regarding a change in one of the active ingredients has been granted. If the listed drug is a combination product and a petition permitting a change in one of the active ingredients in the generic drug has been granted, then the ANDA must be disapproved if the other active ingredients of the generic drug are not the same as those of the listed drug. Further, ANDA must be disapproved in such a circumstance if the different active ingredient in the generic drug is not a listed drug or if the different active ingredient is a drug within the requirements of section 201(p) of the FFDCIA.

Fourth, an ANDA for a drug which is the same must be disapproved if it does not show that the route of administration, dosage form, or strength of the generic drug are all the same as those of the listed drug. If the route of administration, dosage form, or strength of the generic drug differs from that of the listed drug, an ANDA must be disapproved if no petition regarding the change was granted.

Fifth, an ANDA must be disapproved if the generic drug differs from the listed drug and a petition regarding the change has been

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granted, but the ANDA does not contain all of the additional information that the FDA required in granting the petition.

A sixth ground requiring disapproval of an ANDA for a generic drug whose active ingredients are the same as those of the listed drug is that there is unsufficient information to show that the generic drug is bioequivalent to the listed drug. If a petition regarding a change in one of the active ingredients in a combination generic drug has been granted, then the ANDA must be disapproved if the application fails to show that the active ingredients of the generic drug are of the same pharmacological or therapeutic class as those of the listed drug. In addition, such an ANDA must be disapproved if it fails to show that the differing generic combination drug can be expected to have the same therapeutic effect as the listed combination product when administered to patients for an approved condition of use.

Seventh, an ANDA must also be disapproved if it fails to show that the proposed labeling for the generic drug is the same as that of the listed drug. Changes in the proposed labeling due to the fact that the generic drug is produced or distributed by a different manufacturer are not a grounds for disapproval. Similarly, changes in the proposed labeling of the generic drug because a petition regarding a change has been granted is not a grounds for disapproval.

Eighth, an ANDA must be disapproved if it or any other information before the FDA shows that the inactive ingredients of the generic drug are unsafe for use under the conditions prescribed, recommended, or suggested in the proposed labeling for the generic drug. An ANDA must also be disapproved if the composition of the generic drug is unsafe under approved conditions of use. For example, the composition of the generic drug might be unsafe because of the type or quantity of the inactive ingredient included or because of the manner in which the inactive ingredient was included.

Ninth, an ANDA may not be approved if the approval of the listed drug has been withdrawn or suspended for reasons of safety or effectiveness under section 505(e) (1)-(4) of the FFDCA.<sup>11</sup> The ANDA may also not be approved if the FDA determines that the listed drug has been voluntarily withdrawn from the market for safety or effectiveness reasons. The Committee recognizes that the maker of a listed drug might withdraw it from the market without specifying the reason or without articulating safety or effectiveness concerns. For this reason, the Committee authorized the FDA to examine whether safety or effectiveness concerns were one of the reasons for the voluntary withdrawal of the drug from the market. If the FDA so finds, then an ANDA for a generic version of that drug may not be approved.

Tenth, an ANDA may not be approved if it does not meet any of the requirements set forth in paragraph (2)(A). For example, an ANDA that does not contain the certifications regarding patents required in paragraph (a)(A)(vii) cannot be approved.

Last, an ANDA may not be approved if it contains any untrue statement of material fact.<sup>12</sup>

<sup>11</sup> 21 U.S.C. 352(a)(1)-(4).

<sup>12</sup> See Untrue statements in application, 21 C.F.R. 314.12 (1982).



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### *Approval of an ANDA*

Paragraph (4)(A) requires the FDA to approve or disapprove an ANDA within 180 days of initial receipt of the application. The Committee recognizes that extensions may be necessary so the bill permits extensions of this period for so long as the applicant and the FDA may agree upon.

### *Effectiveness of an ANDA approval*

The Committee recognizes that some ANDA's will be submitted and ready for approval before the patent on the listed drug has expired. To deal with this situation and to assure that the FDA concerns itself solely with the safety and effectiveness of the generic drug, paragraph (4)(B) permits the FDA to approve an ANDA but make the approval effective at some later date when appropriate.

If the applicant certified in an ANDA that no patent information was supplied or that the relevant patents have expired, then the approval of the ANDA may be made effective immediately. If the applicant certified based upon the submitted patent information that the patent or patents would expire in one year, then an ANDA may be approved and the approval made effective in one year.

If the applicant certified that one or more of the product or controlling use patents were invalid or not infringed, then approval of the ANDA may be made effective immediately except in the following situation. If within 45 days after notice of the certification of invalidity or non-infringement is received, an action for patent infringement regarding one or more of the patents subject to the certification is brought,<sup>13</sup> then approval of the ANDA may not be made effective immediately. Instead, approval of the ANDA may not be made effective until 18 months after the notice of the certification was provided unless a district court has decided a case for patent infringement earlier. Once either of these events occurs and the approval of the ANDA becomes effective, then the FDA has discharged its statutory responsibility with respect to making the approval of the generic drug effective.

Each party to the action has an affirmative duty to reasonably cooperate in expediting the action. If the plaintiff breaches that duty, the court may shorten the 18 month period as it deems appropriate. If the defendant breaches that duty, the court may extend the 18 month period as it deems appropriate.

If the court decides that the patent is invalid or not infringed before the expiration of the 18 month period (or such shorter or longer period as the court decides), then the approval may be made effective on the date of the court decision. If the court decides that the patent is valid or infringed before the expiration of the 18 month period, then the approval may be made effective on such date as the court orders. The Committee wishes to emphasize that the court may not order an ANDA approved under this provision.

<sup>13</sup> The Committee recognizes that, in certain instances, the patent owner may agree with the certification of the applicant. For example, when the applicant certifies that patent No. 1 is invalid and patent No. 2 is not infringed, the patent owner may agree with the certification regarding patent No. 2. Then an action for patent infringement need only be brought with respect to patent No. 1.



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These are times when approval of an ANDA may be made effective if the FDA has approved the ANDA.

This additional remedy permits the commencement of a legal action for patent infringement before the generic drug maker has begun marketing. The Committee believes this procedure fairly balances the rights of a patent owner to prevent others from making, using, or selling its patented product and the rights of third parties to contest the validity of a patent or to market a product which they believe is not claimed by the patent.

The provisions of this bill relating to the litigation of disputes involving patent validity and infringement are not intended to modify existing patent law with respect to the burden of proof and the nature of the proof to be considered by the courts in determining whether a patent is valid or infringed.

Concern has been expressed that permitting an applicant to market its drug at the conclusion of the 18 month period and possibly before the resolution of the patent infringement suit overturns the statutory presumption of a patent's validity. On the contrary, the Committee intends that a patent would have the same statutory presumption of validity as is afforded under current law.

In most instances, an ANDA will contain multiple certifications. The FDA should make approval of the ANDA effective upon the last certification. For example, if an ANDA contains a certification that a product patent is expired and a controlling use patent will expire in three years, then the FDA must make approval of the ANDA effective in three years. In the case where the patent certification is amended in an ANDA to allege invalidity or non-infringement of a patent, the FDA may not make the approval effective within the 45 day period that an action for patent infringement may be brought.

No action for a declaratory judgment regarding the patent at issue may be brought before the expiration of the 45 day period commencing with the provision of notice of the certification of patent invalidity or non-infringement. Any suit for declaratory judgment after the 45 day period must be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

### *Subsequent ANDA's certifying patent invalidity or noninfringement*

If an ANDA certifying patent invalidity or non-infringement is filed subsequent to an ANDA for the same listed drug that has made the same certification of invalidity or non-infringement, paragraph (4)(B)(iv) provides that the approval of the subsequent ANDA may not be made effective sooner than 180 days after the previous applicant has begun commercial marketing, or the date on which the court holds the patent invalid or not infringed, whichever occurs first. In the event of multiple ANDA's certifying patent invalidity or non-infringement, the courts should employ the existing rules for multidistrict litigation, when appropriate, to avoid hardship on the parties and witnesses and to promote the just and efficient conduct of the patent infringement actions.<sup>14</sup>

<sup>14</sup> 28 U.S.C. 1407.

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### *Disapproval of an ANDA*

If the FDA decides to disapprove an ANDA, paragraph (4)(C) provides that the FDA must give the applicant notice of the opportunity for a hearing on the issue of the approvability of the ANDA. To avail itself of this hearing, the applicant must submit a written request within 30 days of the notice. If a hearing is requested, it must begin not later than 120 days after the notice. However, the hearing may be held later if both the applicant and the FDA agree. The hearing shall be conducted on an expedited basis. The FDA's order regarding the hearing shall be issued within 90 days after the date for filing final briefs.

### *Transition rule*

Paragraph (4)(D)(i) provides that the FDA may not make effective the approval of an ANDA for a drug including an active ingredient (including any ester or salt of the active ingredient) which was approved for the first time in an NDA between January 1, 1982 and the date of enactment of this bill until 10 years after the date of approval of the NDA. For example, if active ingredient X was approved in a drug for the first time in 1983, when the approval of an ANDA for a drug containing active ingredient X could not be made effective until 1993.

### *Unpatentable drugs*

If the active ingredient (including any ester or salt of the active ingredient) of a drug is approved for the first time in an NDA after the enactment of this bill, then paragraph (4)(D)(ii) provides that the FDA may not make the approval of an ANDA for a drug which contains the same active ingredient effective until four years after the approval of the NDA if the following conditions are met.

First, the holder of the NDA must certify that no patent has ever been issued to any person for such drug or for a method of using such drug. Second, the holder must certify that it cannot receive a patent for such drug or for a method using such drug for any known therapeutic purpose. In determining whether a drug meets these two patent stipulations, the FDA may rely upon the certifications of the NDA holder.

If the FDA determines at any time during the four year period that an adequate supply of the drug will not be available, it may make the approval of an ANDA effective before the expiration of the four year period. The FDA may also make the approval of an ANDA for such drug effective before the four year period if the holder of the NDA consents.

### *Withdrawal or suspension of listed drug's approval*

Paragraph (5) provides that the approval of an ANDA is withdrawn or suspended if approval of the listed version of the generic drug has been withdrawn or suspended for safety or effectiveness reasons as set forth in section 505(e) (1)-(4) of the FFDCA. The approval of an ANDA is also withdrawn or suspended if it refers to a drug whose approval is withdrawn or suspended under section 505(j)(5) of the FFDCA. In addition, the approval of an ANDA is withdrawn or suspended if the FDA determines that the listed

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drug has been voluntarily withdrawn from sale due to safety or effectiveness concerns.

The Committee recognizes that the maker of a listed drug might withdraw it from the market without specifying the reason or without articulating safety or effectiveness concerns. For this reason, the Committee authorized the FDA to examine whether safety or effectiveness concerns were one of the reasons for the voluntary withdrawal of the drug from the market. If the FDA so finds, then the approval of an ANDA for a generic version of that drug must be withdrawn or suspended.

The ANDA must be withdrawn or suspended from sale for the same period as the approval of the drug to which it refers has been withdrawn or suspended. When the listed drug has been voluntarily withdrawn from the market and the FDA has determined that the listed drug was withdrawn due to safety or effectiveness reasons, then the approval of the ANDA must be withdrawn until such time as the FDA determines that the listed drug was not withdrawn from sale for safety or effectiveness reasons.

### *Listings of drugs*

Within 60 days after enactment of this bill, Paragraph (6) requires the FDA to publish and to make available a list of drugs eligible for consideration in an ANDA. The list must include the official and proprietary name of each drug that has been approved for safety and effectiveness prior to the date of enactment of the bill. The list must be in alphabetical order. If the drug was approved after 1981, the list must include the date of approval of the drug and the NDA number. Third, the list must specify whether in vitro or in vivo bioequivalence studies, or both, are required for ANDA's.

At 30-day intervals, the FDA must update the list to include drugs that have been approved for safety and effectiveness after enactment of H.R. 3605 and drugs approved in ANDA's under this subsection. In addition, the FDA must integrate into the list patent information submitted under sections 505 (b) and (c) of the FFDCA as it becomes available.

A drug approved for safety and effectiveness under section 505(c) or under subsection (j) shall be considered as published and thus eligible for approval in an ANDA on the date of its approval or the date of enactment, whichever is later.

Paragraph (6)(C) provides a drug may not be listed as eligible for consideration in an ANDA if the approval of the pioneer drug is withdrawn or suspended for safety or effectiveness reasons as set forth in section 505 (e)(1)-(4) of the FFDCA or if approval of the generic drug was withdrawn or suspended under Section 505(j)(5) of the FFDCA. In addition, a drug may not be listed if the FDA determines that the drug has been voluntarily withdrawn from sale due to safety or effectiveness concerns. If such a drug has already been listed, then it must be immediately removed from the list.

The Committee recognizes that the maker of a listed drug might withdraw it from the market without specifying the reason of without articulating safety or effectiveness concerns. For this reason, the Committee authorized the FDA to examine whether safety or effectiveness concerns were one of the reasons for the voluntary withdrawal of the drugs from the market. If the FDA so finds, then

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the drug may not be listed. Persons adversely affected by this decision may seek judicial review under Title 5 of the United States Code.

A drug may not be listed as long as its approval is withdrawn or suspended. If the drug has been voluntarily withdrawn from the market, then the drug may not be listed until the FDA determines that the drug was not withdrawn from sale for safety or effectiveness reasons. A notice regarding the removal of any drug from the list must be published in the Federal Register.

### *Bioavailability and bioequivalence studies*

As used in this bill, the term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.<sup>15</sup>

A drug shall be considered bioequivalent to a listed drug if the rate and extent of absorption of the generic drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses. A generic drug shall also be considered to be bioequivalent to a listed drug if the extent of absorption of the generic drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the generic drug is intentional, is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.<sup>16</sup>

### *Section 102*

Section 102 of the bill requires that certain patent information be filed with all new NDA's and with all NDA's previously filed but not yet approved. Pending and future NDA's may not be approved unless they contain the appropriate patent information. The FDA shall publish the patent information upon approval of the NDA.

This section also requires that any previously approved NDA be amended within 30 days of enactment of this bill to include certain patent information. The FDA shall publish the patent information upon its submission. An NDA may be revoked if the patent information available is advisable and is not filed within 30 days after receipt of a written notice from the FDA specifying the failure to provide the patent information.

The patent information to be filed includes the patent number and the expiration date of any patent which claims the drug in the NDA or which claims a method of using such drug with respect to which a claim of patent infringement could reasonably be asserted

<sup>15</sup> See Definition of Bioavailability, 21 C.F.R. 320.1(a) (1982).

<sup>16</sup> See Definition of Bioequivalent Drug Products, 21 C.F.R. 320.1(e) (1982).